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Review

In silico neuronal morphology classification: A systematic review

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ABSTRACT

Advances in connectomics and the characterization of neuronal diversity have been fundamental to understanding how the brain works. Defining a taxonomy is still challenging and requires complex computational methods. In this paper, we present a systematic review of the state-of-the-art methods for neuronal morphology classification, shedding light on trends and future directions. We address three core research questions: (1) What computational methods are used to classify neuronal morphologies? (2) What kind of representation do the classification models work on? (3) How are the classification models evaluated? We applied a structured protocol including peer-reviewed studies published since 2018. We collected 840 papers from five databases, published between 2018 and 2024. We assessed risk of bias using predefined quality criteria on study design, methodology, and reporting; 35 studies met these standards and were included to extract information and consolidate the results. The results show that Artificial Neural Networks are currently the main method for classifying neurons based on morphometric features (21 papers). Representations based on microscopy images for extracting morphometric features (30) are commonly used. Accuracy (29) is the predominant evaluation measure. Our research findings contribute to the body of knowledge by providing an up-to-date perspective on neuronal classification, which can guide future research in neuroscience and related fields.

Introduction

What are the shapes of the thoughts? This question is driving a revolution in neuroscience, known as high-throughput neural circuit reconstruction or connectomics (Galili et al., 2022; Beyer et al., 2022). Despite the promising prospects and recent advances, many challenges still prevent connectomics from becoming a reality on a wider scale (Beyer et al., 2022; Kumar et al., 2025). Some remaining barriers include classifying neuronal types, integrating multimodal neuronal data, and standardizing large-scale datasets. This multimodality revealed that cell types in the brain and the body exhibit diverse properties regarding molecular, morphological, physiological, and functional aspects (Zeng, 2022; Peng et al., 2021; Andriatsilavo and Hassan, 2025). While neuron cell classification approaches based on transcriptomics have recently significantly enlarged the repertoire of available methods, descriptors of brain structure, such as the distribution, morphology, and synaptic connectivity of neuronal cell types across brain regions, are the most likely to explain the brain's information processing capacity (Zeng, 2022; Khalil et al., 2022). According to Zeng (2022), for a definition of cell types to be meaningful, it must be associated with what cell types do, so transcriptomic cell type taxonomy must be linked to anatomical and functional information to evaluate the validity of the transcriptomic taxonomy and determine the appropriate level of granularity.

Brain-wide complete reconstruction of single-neuron morphology is currently the only approach to capture the full extent of a neuron's axon projection pattern and define projection neuron types (Zeng, 2022; Gao et al., 2022; Peng et al., 2021). Morphometry is also helpful in identifying the effects of neurotoxic substances on neurodevelopment (Gill and Kumara, 2021). In addition to the abovementioned applications, the literature also contains works that report cellular morphometric analysis to provide insights into age-related changes (Stojić et al., 2021a), plasticity (Lv et al., 2025), ontogenesis (Porceddu et al., 2024), and even comparative analysis of neurons between species and brain regions (Khalil et al., 2022). Morphometric characteristics can serve as essential markers for understanding how structural differences at the cellular level influence brain activity and contribute to variability in behaviors and cognitive functions, whether in physiological or pathological states. Therefore, it is essential to highlight and systematically analyze how these morphometric features are represented computationally to tackle some of the challenges of neuron type classification.

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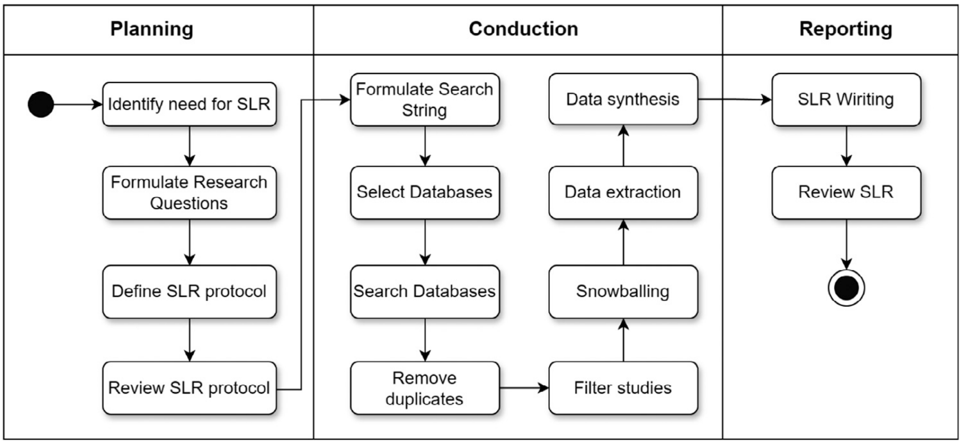

Fig. 1. Flow diagram of the systematic literature review process, organized in the three phases: planning, conduction, and reporting.

Even after more than a century of research on neural circuits (Cajal, 1899), a significant gap remains in our understanding: How many different types of neurons exist? To address this question, international efforts such as the Human Brain Project (Mahfoud, 2021), and the BRAIN initiatives (Insel et al., 2013) have outlined neuronal classification as one of their priorities. Fundamentally, a neuron type is a testable hypothesis, where similarity indicates functional equivalence (Zeng, 2022; Mukamel and Ngai, 2019). Following this rationale, neurons with the same anatomical characteristics belong to the same type, performing the same function. Consequently, the quantitative neuron characterization from digital reconstructions is crucial for investigating anatomical comparisons and cell morphometric analyses (Leite et al., 2024). These reconstructions are available in worldwide accessible repositories such as NeuroMorpho.org (Ascoli et al., 2007) and Allen Cell Types (Hawrylycz et al., 2012). Recently, there has been a significant paradigm shift in neuronal classification, with the adoption of automatic quantitative methods based on morphometric features (Zhao et al., 2022). Both supervised and unsupervised Machine Learning (ML) models have gained prominence in this context. These methods provide a systematic and objective approach to identifying distinct neuronal types, offering a quantitative and unbiased analysis. Unlike more traditional approaches, these methods offer a more refined and detailed understanding of neuronal complexity, enabling more precise classification (Batabyal et al., 2020).

This paper presents a Systematic Literature Review (SLR) that examines a broad set of papers drawn from various digital libraries. After careful selection and evaluation, a final set of studies was established, forming the basis for extracting information and synthesizing the results. Before stating the research goal, some terminology clarification is needed. In this paper, morphometric features means quantitative measures extracted from neuronal morphologies (e.g. dendrite length, number of branches, branching angles, etc.); topological features cover structural characteristics describing spatial organization and connections within neurons and neural networks; electrophysiological features refer to the neurons' electrical properties, including parameters such as resting potential and duration of action potentials; finally, morphological classification refers to classifying neurons based on morphometric features.

With these definitions in mind, the main goal of our study was to investigate the automatic approaches for classifying neuronal morphologies. Besides, the different neuron representation formats found in the literature, and a critical evaluation of the performance measures were examined. We identified emerging trends and patterns in automated neuronal classification. Our comprehensive analysis provided a deeper understanding of the computational strategies used. This analysis offered insights into the primary data sources, the species from which the morphologies originated, their anatomical locations, and the various morphological types. For better readability and in accordance with open science principles, we have made supplementary material available on GitHub,[1] including a list of acronyms to facilitate reading, complementary results, additional images to aid data visualization, and the databases and source code used.

The remainder of this paper is organized as follows. In Section "Research methodology", we present the systematic review protocols adopted. The results obtained are described in Section "Results" and discussed in Section "Discussion". Finally, the conclusions and suggestions for future work are presented in Section "Conclusions".

Research methodology

The review followed the guidelines proposed by Kitchenham and Charters (Kitchenham and Charters, 2007). Fig. 1 provides an overview of the systematic literature review process, which was divided into three phases: planning, conducting, and reporting. As a starting point, we analyzed the state of the art, identifying a knowledge gap regarding the need for an SRL in *in silico* methods for classifying neurons based on their morphology. For this purpose, we formulated the RQs and defined the protocol to be adopted, which was reviewed and approved by all the authors. During the conduction phase, we formulated the search strings and selected the bibliographic databases (see below) that were most relevant to our study topic.

After applying the search queries, all the studies found were collected and imported into Parsifal, where duplicates were removed. Through multiple interactions, the studies were filtered based on predefined criteria. Additionally, we applied the Snowball Sampling method to identify additional highly relevant primary studies (Wohlin, 2014). At this point, we used three quality criteria to evaluate the studies, resulting in 35 studies for analysis, listed in Table 4. The extraction and synthesis activities were conducted and reviewed by three independent authors. We compiled this artifact to include all significant findings during the final documentation stage. The following subsections describe the research methodology in detail.

Population, intervention, comparison, outcome, context

The Population, Intervention, Comparison, Outcome, Context (PICOC) method was adopted to inform the formulation of research questions and the design of the search string. Using PICOC, we defined neuronal morphologies as the population, classification as the intervention, methods/representations/evaluation as comparison, and neuroscience/neuroinformatics as context. Based on these PICOCs, the research questions presented below were defined.

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[1] https://github.com/fabiolobato/in_silico_neuronal_classification

Table 1
The list of inclusion and exclusion criteria used to select the studies.

Inclusion criteria
IC1: Papers published since 2018; IC2: Peer-reviewed papers from journals and relevant conferences; IC3: Publications that propose or compare methods for classifying neuronal morphologies.
Exclusion criteria
EC1: Book chapters, review papers, master's and doctoral theses, textbooks, websites, and unfinished work; EC2: Tutorial slides, short papers, posters, and technical reports; EC3: Editorials and opinion papers; EC4: Papers published in languages other than English; EC5: Duplicated publications; EC6: Publications that do not suit the RQs.

Research questions

The main goal was to identify which methods are used to classify neuronal morphologies and to compare the neuronal representation types reported in the literature. These objectives allowed us to outline the following research questions:

- **RQ1:** What computational methods are used to classify neuronal morphologies?
- **RQ2:** What kind of representation do the classification models work on?
- **RQ3:** How are the classification models evaluated?

RQ1 was formulated to identify the computational methods currently being employed in classifying neuronal morphologies. These methods include machine learning techniques, image analysis, and pattern recognition algorithms, among others, used to identify and differentiate among neuronal morphologies. RQ2 complements RQ1 by examining the different types of neural representations used in classification models, such as graph-based, image-based, and others. Based on the answer to RQ2, we can provide insights into how neurons are modeled. Finally, RQ3 focuses on the evaluation methods used to validate the models, including performance measures such as precision and F1-score, as well as Area Under the Curve (AUC) analysis. These metrics are essential for determining the reliability and usefulness of the generated classifications. This study aims to contribute to a more comprehensive understanding of current approaches to *in silico* classification of neuronal morphologies by addressing these questions.

Study selection

We developed selection criteria to refine our SLR, aiming to disconsider studies that are not relevant to the topic of interest. Table 1 presents the Inclusion Criteria (IC) and Exclusion Criteria (EC) applied.

This review targeted papers published between 2018 and 2024 (IC1). Initially, a five-year time frame was established, from 2018 to 2022. However, as the project progressed, we included subsequent years and decided not to remove the previously analyzed works, as they incorporate valuable insights from the research field. These works had to be published in peer-reviewed journals and conferences (IC2). As the final Inclusion Criterion, the articles needed to align with the study's objective by proposing or comparing methods for classifying neuronal morphologies (IC3). Regarding the Exclusion Criteria, specific publication formats were excluded (EC1, EC2, and EC3). Publications in languages other than English were excluded (EC4), aiming to ensure linguistic consistency. Because automated searches sometimes produce errors, the papers were verified both manually and automatically after collection to remove duplicates (EC5). Finally, publications that would not contribute to answering the research questions were excluded (EC6). These criteria were applied to all papers to select the most relevant. Any doubts during the study filtering process were discussed and resolved among the authors. This collaborative approach ensured consistency, reliability, and potential replicability of the selection. It is essential to note that IC3 and EC6 are related to the Quality Assessment (QA) questions.

Table 2
Search syntax and keywords used in ACM Digital Library, IEEE Xplore, ISI Web of Science, Science Direct, and Scopus.

Databases	Search strings
ACM Digital Library	*[[All: "neuronal morphologies"] OR [All: "neuronal cell-type"] OR [All: "neuronal morphology"]] AND [[All: "classification"] OR [All: "classifier"] OR [All: "classifiers"] OR ["supervised learning"]]*
IEEE Xplore	*(("All Metadata":neuronal morphologies OR "All Metadata":neuronal cell-type OR "All Metadata":neuronal morphology) AND ("All Metadata":classification OR "All Metadata":classifier OR "All Metadata":classifiers OR "All Metadata":supervised learning))*
ISI Web of Science	*ALL=(("neuronal morphologies" OR "neuronal cell-type" OR "neuronal morphology") AND ("classification" OR "classifier" OR "classifiers" OR "supervised learning"))*
Science Direct	*("neuronal morphologies" OR "neuronal cell-type" OR "neuronal morphology") AND ("classification" OR "classifier" OR "classifiers" OR "supervised learning")*
Scopus	*TITLE-ABS-KEY (("neuronal morphologies" OR "neuronal cell-type" OR "neuronal morphology") AND ("classification" OR "classifier" OR "classifiers" OR "supervised learning"))*

Search strategy

The search strategy was carefully designed to ensure comprehensiveness and accuracy in identifying papers within our scope. The following base search string was created: **("neuronal morphologies" OR "neuronal cell-type" OR "neuronal morphology") AND ("classification" OR "classifier" OR "classifiers" OR "supervised learning")**. This string was adapted for each database and is presented in Table 2. The bibliographic databases selected to find the publications were: ACM Digital Library,[2] IEEE Xplore,[3] ISI Web of Science,[4] Science Direct,[5] and Scopus.[6] The final data import from these databases was performed in February 2024.

Using the search strings in the five selected bibliographic databases identified a total of 840 publications (see Table 3). We used the standard search only for ScienceDirect, whereas we applied the advanced search to the ACM Digital Library, IEEE Xplore, ISI Web of Science, and Scopus databases. We also applied filters for period, publication type, and language to further refine the publication collection. Each search result across all databases was exported in BibTeX format and imported into Parsifal, where we manually and automatically removed 43 duplicate publications. The remaining 797 papers were subjected to additional filtering, described in the following subsection.

Three independent reviewers filtered potentially relevant papers. This process was based on reading the title, abstract, and, when necessary, the full text, in accordance with the established Inclusion and Exclusion Criteria. The selection process was facilitated by the Parsifal environment, which enabled reviewers to annotate papers in the following categories: "duplicate", "rejected", or "accepted". The results

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[2] https://dl.acm.org/
[3] https://ieeexplore.ieee.org/
[4] http://isiknowledge.com/
[5] https://www.sciencedirect.com/
[6] https://www.scopus.com/

Table 3
Database search yields and initial screening results, detailing the number of duplicate, rejected, and accepted papers per database.

Databases	Results	Duplicate	Rejected	Accepted
Scopus	66	21	31	14
Science Direct	665	6	644	15
ISI Web of Science	71	9	43	19
IEEE Xplore	34	7	21	6
ACM	4	0	4	0
Total	840	43	743	54

of this process are summarized in Table 3, which presents the number of publications per database.

Our analysis considered not only the initial results but also the duplicates identified and the publications rejected throughout the filtering process. Only a limited portion (6.4%) were accepted. A noteworthy observation is the varied performance of the search mechanism across different databases, highlighting the importance of using multiple sources during the review process to ensure a comprehensive and diverse representation of the literature in our research. We supplemented the initial search with the manual addition of relevant literature to obtain a more significant number of papers in the bibliographic search, following the guidelines of the Snowballing method described by Wohlin (2014). In this study, *backward snowballing* and *forward snowballing* were conducted on the 54 accepted papers. The first approach involved analyzing the references in the selected papers, while the second consisted of checking new studies that cited these papers. These methods were repeated iteratively until no new relevant papers were found. Once the process was complete, 2 additional studies were identified and included as a result of the manual search. Thus, the total number of papers that proceeded to the Quality Assessment (QA) increased to 56.

Quality assessment

After filtering, we organized a checklist to verify the quality of the selected papers (Kitchenham and Charters, 2007). Subsequently, the risk of bias was assessed using predefined quality criteria on study design, methodology, and reporting. Three QA questions were defined, as shown below:

- **QA1:** Does the paper clearly and thoroughly describe the proposal or comparison of method(s) for classifying neurons based on their morphology?
- **QA2:** Are the neuronal morphology representations used in the experiments described?
- **QA3:** Are the evaluation measures/strategy clearly defined?

The questions were scored on a **3** point scale, with scores ranging from “yes” (1.0), “partly” (0.5), and “no” (0.0). However, to be included in our review, the publications needed to achieve a score of 2.0 or higher, as this indicates that the study can answer the research questions. From this stage onwards, we used Mendeley[7] to manage the references, which provided greater fluidity and efficiency in organizing and accessing the papers. Table 4 presents the quality assessment scores. As noted, 35 papers achieved a score equal to or higher than 2. This indicates that they met the quality evaluation criteria, signifying their acceptability. These papers provided relevant insights for addressing our research questions and were thus considered for extracting pertinent information, as described below.

Data extraction and synthesis

After the studies were selected, the relevant data were extracted from each paper. To ensure comprehensive and organized data collection, a form was developed. This form was not a rigid template, but rather a flexible tool that could be adapted to the specific research questions. It enabled the creation of a collaborative spreadsheet, allowing the authors to discuss and resolve any questions or discrepancies identified during the process.

As presented in Table 5, the form included general aspects – metadata – and particular characteristics, such as data sources, types of neurons, brain regions, and species. The form included specific aspects such as types of neural morphology representations, classification methods, neuroscience tools, source-code availability, programming language, and metrics for evaluating the results. For this, a thorough and complete re-reading of the studies was conducted to obtain a descriptive assessment. However, in cases where the aspect was not mentioned, we annotated it as “not described”.

After extracting the information, a script was developed in the Python 3 programming language to conduct the exploratory analysis. The process used libraries such as Pandas and Matplotlib for data manipulation and visualization. Preprocessing was performed to standardize and clean the data. This included stages such as converting all words to lowercase to avoid discrepancies due to different capitalization forms and removing accentuation, which could cause inconsistencies in later analyses. Additionally, unnecessary blank spaces were eliminated, creating a more organized and coherent structure. Finally, we consolidated the results, which are presented in Section “Results”.

Results

This section presents the results according to the protocol detailed above. First, we provide an overview of bibliometric information. Next, the research questions are addressed, with detailed findings on computational methods, morphological data representations, and performance measures. Considering the analyses performed and aiming to contribute to the body of knowledge in neuroscience, a detailed description of the databases in relation to species, brain regions, and cell types is provided at the end of the section. Supplementary material with extra results is available on https://github.com/fabiolobato/in_silico_neuronal_classification.

Overview

Fig. 2 summarize the publication distribution over the years. Notably, there has been a relatively even study distribution over recent years on the neuronal morphology classification using automated methods, as shown in Fig. 2. In recent years, there has been a slight upward trend in publications about neuronal classification using *in silico* methods. The decline in 2023 can be conjectured by the fact that the COVID-19 pandemic period has impacted several areas in biomedicine, considering that research efforts have also been directed toward assessing the impact of COVID-19 and its neuronal manifestations (Aghagoli et al., 2021; Montalvan et al., 2020).

As defined in our protocol, studies may be drawn from either conferences or journals. However, the vast majority of studies are published in journals, accounting for more than 77%. The computer science research field acknowledges conferences, evidenced by Google Scholar[8] metrics, which display three conferences in the top 10 publications. The “*IEEE/CVF Conference on Computer Vision and Pattern Recognition*” (h-index: 440) is worth mentioning, which is higher than The New England Journal of Medicine, Science, or The Lancet. On the other hand, neuroscience acknowledges journals considering its roots in more mature research fields (e.g., biology, medicine, and biotechnology). These exploratory results were useful for validating the proposed systematic review protocol and for demonstrating that *in silico* neuronal morphology classification is a promising research topic, as recent advancements in machine learning and neuronal reconstruction have demonstrated. This is presented in the following sections.

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[7] https://www.mendeley.com/search/

[8] https://scholar.google.com/citations

Table 4
Quality assessment scores per paper, considering the QA's defined.

Reference	QA1	QA2	QA3	Score	Reference	QA1	QA2	QA3	Score
P1 (Lin and Zheng, 2018)	0.5	1.0	1.0	2.5	P29 (He et al., 2022)	1.0	1.0	1.0	3.0
P2 (Kunst et al., 2019)	0.0	0.5	0.0	0.5	P30 (Ophir et al., 2023)	0.5	0.5	1.0	2.0
P3 (Buccino et al., 2018)	0.5	0.5	0.5	1.5	P31 (Vecchi et al., 2021)	0.0	1.0	0.0	1.0
P4 (Sharma et al., 2019)	0.0	0.5	0.5	1.0	P32 (Batabyal et al., 2020)	1.0	1.0	1.0	3.0
P5 (Laturnus et al., 2020)	1.0	1.0	1.0	3.0	P33 (Wei et al., 2023)	1.0	1.0	1.0	3.0
P6 (Kanari et al., 2018)	0.0	1.0	0.5	1.5	P34 (Li et al., 2020)	0.0	0.5	0.5	1.0
P7 (Lin et al., 2018)	1.0	1.0	1.0	3.0	P35 (López-Cabrera et al., 2020)	1.0	1.0	1.0	3.0
P8 (Lin and Zheng, 2019)	1.0	1.0	1.0	3.0	P36 (Kanari et al., 2019)	1.0	1.0	1.0	3.0
P9 (Wang et al., 2018)	0.0	1.0	0.5	1.5	P37 (Barros et al., 2022)	0.5	1.0	1.0	2.5
P10 (Mao et al., 2020)	0.0	0.5	0.0	0.5	P38 (Choi et al., 2023)	0.0	0.0	0.0	0.0
P11 (Troullinou et al., 2021)	1.0	1.0	1.0	3.0	P39 (Nourollah et al., 2024)	0.0	0.0	0.0	0.0
P12 (Gamal et al., 2018)	0.0	0.0	1.0	1.0	P40 (Zheng and Lin, 2019)	1.0	1.0	1.0	3.0
P13 (Mata et al., 2019)	0.5	1.0	1.0	2.5	P41 (Krstonošić et al., 2023)	0.0	0.5	0.0	0.5
P14 (Beers et al., 2023)	0.0	1.0	0.0	1.0	P42 (Nandi et al., 2022)	0.0	1.0	0.0	1.0
P15 (Stojić et al., 2021b)	1.0	1.0	1.0	3.0	P43 (Kirch and Gollo, 2020)	0.0	1.0	1.0	2.0
P16 (Yang et al., 2021)	0.5	1.0	1.0	2.5	P44 (Milosević et al., 2019)	0.0	0.5	0.0	0.5
P17 (Xiong et al., 2024)	1.0	1.0	1.0	3.0	P45 (Grbatinić et al., 2018)	1.0	1.0	0.5	2.5
P18 (Zhu et al., 2023)	1.0	1.0	1.0	3.0	P46 (Khalil et al., 2022)	0.0	1.0	1.0	2.0
P19 (Grein et al., 2020)	0.0	1.0	0.0	1.0	P47 (Liao et al., 2023)	0.0	0.0	0.0	0.0
P20 (He et al., 2023)	1.0	1.0	1.0	3.0	P48 (Chen et al., 2022)	0.5	1.0	1.0	2.5
P21 (Lopez-Cabrera and Lorenzo-Ginori, 2018)	1.0	1.0	1.0	3.0	P49 (Reilly et al., 2020)	0.0	0.0	0.0	0.0
P22 (Zhao et al., 2022)	1.0	1.0	0.5	2.5	P50 (Jiang et al., 2023)	1.0	1.0	1.0	3.0
P23 (Peach et al., 2021)	1.0	1.0	1.0	3.0	P51 (Zhang et al., 2021)	1.0	1.0	1.0	3.0
P24 (Li et al., 2019)	0.0	0.0	1.0	1.0	P52 (Ophir et al., 2024)	1.0	1.0	1.0	3.0
P25 (Hiatt et al., 2022)	0.5	1.0	0.5	2.0	P53 (Sun and Zhao, 2024)	1.0	1.0	1.0	3.0
P26 (Gouwens et al., 2020)	0.0	1.0	0.5	1.5	P54 (Liao et al., 2024)	1.0	1.0	1.0	3.0
P27 (Ljungquist et al., 2022)	0.0	1.0	0.5	1.5	P55 (He et al., 2024)	1.0	1.0	1.0	3.0
P28 (Friedman, 2020)	0.5	1.0	0.5	2.0	P56 (Kanari et al., 2024)	1.0	1.0	1.0	3.0

Table 5
List of the 10 aspects extracted from each study and their descriptions, including data source, morphologies representation, and classification methods.

Aspects	Description
Paper/work metadata	Refers to the basic information of the paper, such as title, authors, publication year, and journal/conference.
Data source	The data source for neuronal morphologies, which may include worldwide accessible databases.
Cell type	The type(s) of the neuronal cell(s) used in the classification tasks.
Brain region	The brain region to which the studied morphologies correspond.
Species	The animal species or biological model used in the study.
Morphologies representation	The way morphologies are represented in the study for possible feature extraction and classification.
Classification methods	Methods used to classify or categorize neuron morphologies (e.g., machine learning algorithms).
Neuroscience tools	Specific neuroscience tools used in the study.
Available code	Indication whether the source code is available for access or download.
Programming language	The programming language used to develop the code mentioned in the study (if applicable).
Evaluation measures	The evaluation measures used to assess classification method performance.

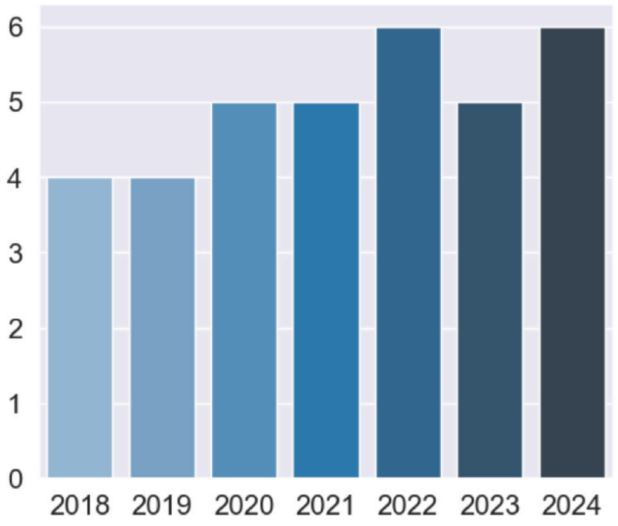

Fig. 2. Distribution of the included publications by their year of publication.

Computational methods

In this subsection, we answer the *RQ1: What computational methods are used to classify neuronal morphologies?* In accordance with Batabyal et al. (2020), the motivation behind this question is that it is practically impossible to identify and categorize a trillion neuronal cells manually or with semiautomatic methods. Most studies compare different methods, as in Barros et al. (2022), who applied Support Vector Machine (SVM), Decision Tree (DT), Random Forest (RF), and Artificial Neural Networks (ANN). Despite the relevance of developing classification models for neuronal morphologies, there is no literature dedicated to systematically mapping and reviewing these methods. In an effort to fill this gap, we contribute to the body of knowledge by identifying various computational methods used to classify and/or categorize neurons based on their morphologies. We also explore beyond the RQ1 by briefly explaining the basic principles of mainstream methods and discussing the strengths and weaknesses of each method.

Fig. 3 summarizes the most commonly used computational methods. Our results show that ANNs emerge as the predominant approach, accounting for 60% of the methods used in the studies. This preference can be attributed to the ability of neural networks to learn complex patterns and extract deep features from data, making them a natural choice for neuron morphology classification tasks. In addition to ANNs, other popular methods include SVM, K-Nearest Neighbors (K-NN), RF, DT, Logistic Regression, Naïve Bayes, K-Means, eXtreme Gradient Boosting (XGBoost), and Linear Discriminant Analysis (LDA), which demonstrate their relevance and applicability in this context. In the next subsections, we present the taxonomy of classification methods,

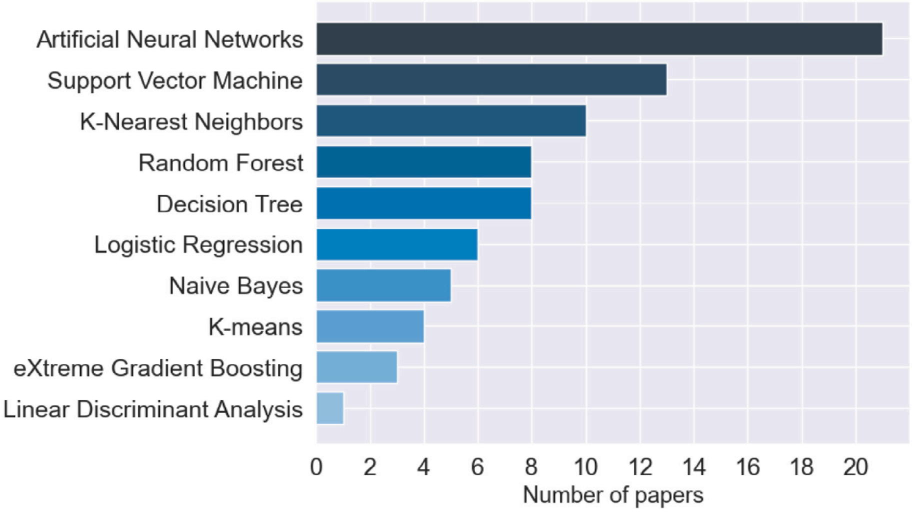

Fig. 3. Top 10 classification methods most commonly used.

followed by an explanation of the methods' intuition, and an overview of deep learning methods.

Classification methods taxonomy

According to Luengo et al. (2012), the classification methods can be categorized into three groups, to know: (i) *rule induction learning*, this group refers to algorithms that infer rules using different strategies. (ii) *approximate models*, this category embraces black box methods such as neural networks, support vector machines, and statistical learning (e.g., Naïve Bayes). Although the Naïve Bayes method is not a completely black box method, Luengo et al. (2012) have considered this the most appropriate category for it; finally, (iii) *lazy learning*, which includes methods that do not create any model but use the training data to perform the classification directly. In this sense, it is possible to attest that all categories are used for classifying neurons based on their morphologies, as shown in Table 6.

Table 6 reveals that *Rule Induction Learning* is reported in 11 papers. Only two methods appear to be known: Random Forest and Decision Tree. These methods are considered white-box or glass-box models (interpretable). This interpretability is highly interesting for neuroscience research, as it enables identification of which morphometric features are most sensitive for classifying neurons, given the discordance in classification among human experts, as pointed out by DeFelipe et al. (2013). It is also possible to analyze the correlation between different morphological types (e.g., pyramidal cells and interneurons) and functional types (e.g., excitatory and inhibitory).

Lazy Learning category is also considered in 14 papers, represented by K-NN and K-Means; the latter is an unsupervised learning method (Ahmed et al., 2020). However, the authors use K-Means in combination with other machine learning methods to classify neurons based on their morphology. Sometimes, supervised and unsupervised learning are integrated into semisupervised learning, where a small amount of labeled data is combined with large amounts of unlabeled data, thereby improving classification performance when labeled data are costly to obtain Greener et al. (2022). Despite not being explainable *per se*, Lazy Learning methods exhibit stable performance on small datasets (less than 100k examples).[9] It is also presented in the Scikit-learn framework tutorial for "Choosing the right estimator" - see https://scikit-learn.org/1.6/machine_learning_map.html. Its parameterization is also well consolidated in the literature, making it easy to be adopted by non-experts in machine learning - a common scenario in multidisciplinary research fields such as neuroscience (Greener

Table 6
In silico neuronal classification methods categorization, presenting the methods per categories and the corresponding papers.

Category	Methods	Papers
Rule induction learning	Random Forest and Decision Tree	Hiatt et al. (2022), Zheng and Lin (2019), Xiong et al. (2024), Ophir et al. (2023), Lopez-Cabrera and Lorenzo-Ginori (2018), López-Cabrera et al. (2020), Barros et al. (2022), Mata et al. (2019), Laturnus et al. (2020), Lin and Zheng (2019), Kanari et al. (2024)
Lazy learning	K-Nearest Neighbors and K-Means	Batabyal et al. (2020), Laturnus et al. (2020), Lin and Zheng (2019), Lin et al. (2018), Lopez-Cabrera and Lorenzo-Ginori (2018), López-Cabrera et al. (2020), Mata et al. (2019), Khalil et al. (2022), Hiatt et al. (2022), Zheng and Lin (2019), Grbatinić et al. (2018), Stojić et al. (2021b), Friedman (2020), Jiang et al. (2023)
Approximate models	Neural Networks, Support Vector Machine, Logistic Regression, Naïve Bayes, Linear Discriminant Analysis, and XGBoost	Grbatinić et al. (2018), Lin et al. (2018), Lin and Zheng (2019, 2018), Troullinou et al. (2021), Barros et al. (2022), Yang et al. (2021), Hiatt et al. (2022), Chen et al. (2022), Zhu et al. (2023), He et al. (2023, 2022), Wei et al. (2023), Xiong et al. (2024), Zhang et al. (2021), Ophir et al. (2023), Batabyal et al. (2020), López-Cabrera et al. (2020), Lopez-Cabrera and Lorenzo-Ginori (2018), Zhao et al. (2022), Zheng and Lin (2019), Sun and Zhao (2024), Ophir et al. (2024), Liao et al. (2024), He et al. (2024)

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[9] This heuristic is widely used in the ML community.

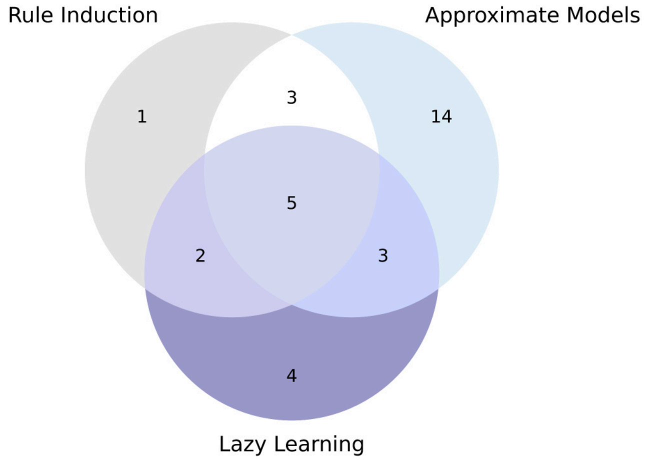


Fig. 4. Venn Diagram based on ML methods categories found in the reviewed literature, demonstrating the intersection between them.

et al., 2022; Badrulhisham et al., 2024). Rule Induction and Lazy Learning methods are frequently used as baselines due to their simplicity, interpretability (in the case of Rule Induction), and ease of implementation.

Approximate Models are gaining more attention due to Deep Learning (DL) and Boosting algorithms being used in 25 papers. Neural Networks, Support Vector Machine, Logistic Regression, Naïve Bayes, Linear Discriminant Analysis, and XGBoost are included in this category. Most of them are considered *black-box*. To deepen our understanding of ML in neuronal morphology classification, we analyzed the co-occurrence of these categories, as shown in Fig. 4.

Analyzing Fig. 4, it is possible to attest that *Rule Induction Learning* is only used alone in one paper, corroborating that these methods are routinely used as baselines. Only four papers use exclusive *Lazy Learning* methods, compared to 14 papers that use exclusively *Approximate Models*. A total of 5 works used all categories. These findings highlight the growing adoption of multiple supervised learning paradigms. It is crucial to point out that the performance of deep learning methods is sensitive to data volume (Badrulhisham et al., 2024).

Regarding *Approximate Models*, most papers employ neural networks with deep learning architectures. This ML paradigm was proposed in 2012 and achieved breakthroughs in speech and visual recognition (Zhang and Lu, 2021). Deep learning discovers data distribution characteristics by combining low-level features to form high-level attribute categories or features (Shokri and Shmatikov, 2015; Zhang et al., 2019; Borisov et al., 2022). Deep learning can be a powerful tool and is currently highly popular. The usage of DL methods is quite thrilling in neuroscience (Richards et al., 2019). For instance, Goldstein et al. (2022) investigated shared computational principles between the way the human brain and DL methods process natural language; Vallabhaneni et al. (2021) reviewed the application of DL algorithms to decode the physiological or pathological state of the brain from electroencephalography; and Chattopadhyay and Maitra (2022) proposed an algorithm to segment brain tumors from Magnetic Resonance brain Images by a Convolutional Neural Network.

Methods' intuition

We present here a brief explanation of the basic principles of mainstream methods used for *in silico* neuronal classification. A broader overview is provided by Sarker (2021). **Decision Trees** recursively split the dataset into subsets based on feature values, forming a tree-like structure of decision rules. DTs are human-readable, intuitive "if-then" rules presented as a tree, allowing interpretation of how a decision is made. Moreover, the DT parameterization is well established in the ML literature. **Random Forests** enhance the predictive power and stability of decision trees by combining multiple trees into a single model. It employs an ensemble strategy to improve model performance by combining weak classifiers into a more robust and stable model. Decision Trees are simple but interpretable models that may overfit the data. On the other hand, Random Forests offer better generalization at the cost of reducing interpretability.

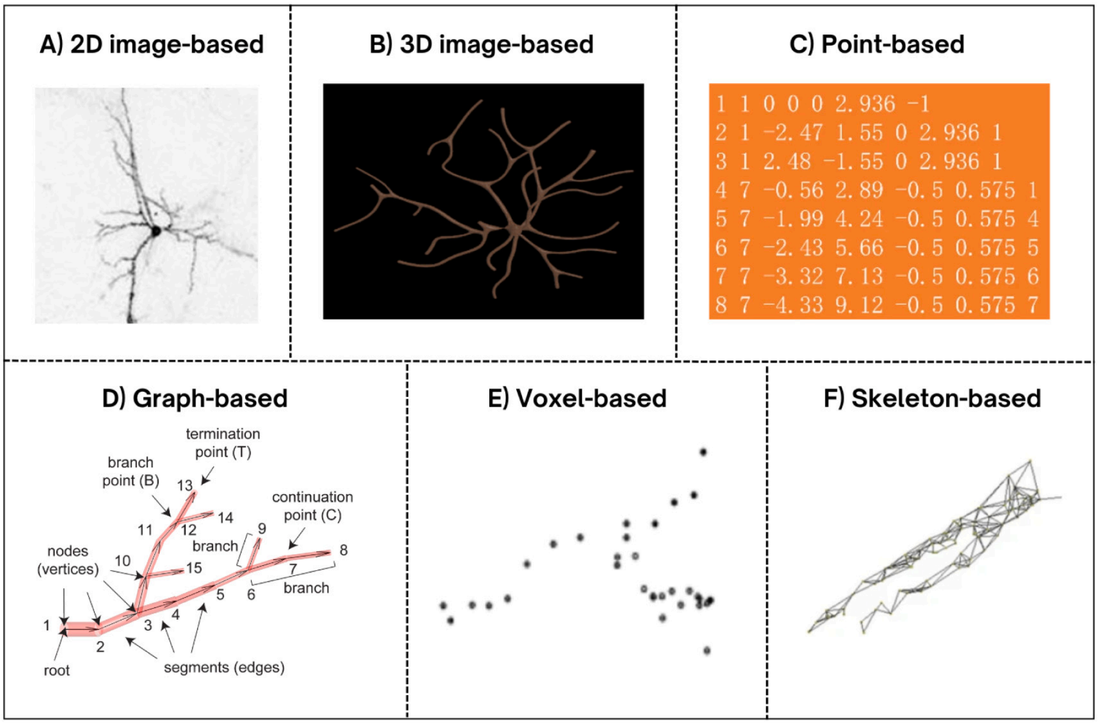
K-Nearest Neighbors is one of the simplest classification approaches. It is considered a lazy machine learning method because it does not involve explicit model construction. To classify a new instance, the database is consulted, and the K nearest neighbors within the dimensional space of the attributes are computed. **K-Means** is an unsupervised machine learning method and a general-purpose algorithm for data clustering. The algorithm partitions the dataset into K clusters, where each data point belongs to the cluster whose centroid is nearest to it. The algorithm minimizes the within-cluster sum of squared distances to group similar data points.

Naïve Bayes is based on Bayes' theorem with the "naïve" assumption of conditional independence between every pair of features given the value of the class variable. These models also require low computing resources since their training is faster than more sophisticated methods. **Logistic Regression** is considered a fundamental algorithm used primarily for binary classification. This algorithm models the probability that an instance belongs to a particular class using a logistic (sigmoid) function. **Linear Discriminant Analysis** is a supervised machine learning algorithm closely related to logistic regression, but differs in its assumptions and optimization approach. LDA aims to find a linear combination of features that best separates two or more classes by fitting class-conditional densities to the data and applying Bayes' rule. **Support Vector Machine** operates by finding an optimal hyperplane that separates data points into distinct classes in a high-dimensional space. The intuition behind SVM is to maximize the margin between the nearest data points of each class and the hyperplane, known as the support vectors.

XGBoost is based on the gradient boosting framework. Similar to Random Forest, XGBoost builds an ensemble of decision trees. The ensemble is built sequentially, with each tree correcting the errors of its predecessor. XGBoost handles structured tabular data effectively and is also scalable. **Artificial Neural Networks** are computational models inspired by the human brain's structure and functioning. They consist of interconnected units called neurons, which process information through activation and deactivation. Their emergence dates back to the perceptron model proposed by McCulloch and Pitts, where neurons receive multiple inputs $X = \{x_1, x_2, \dots, x_n\}$, each weighted by synaptic weights (w), and compute a weighted sum. An activation function determines the neuron's activation. Training an ANN involves adjusting these weights, which serve as the model's parameters and store its learned knowledge.

Deep learning methods

The requirement for large amounts of data can render deep learning a poor choice even when the other two requirements are met, as in *in silico* neuronal morphology classification, where NeuroMorpho.org provides 261,316 3D digital reconstructions. We found that deep learning models are being tested for neuronal classification. Long Short-Term Memory (LSTM), Residual Network (ResNet), and Convolutional Neural Network (CNN) are prominent architectural frameworks in neuronal morphology classification. The LSTM architecture is known for its ability to handle temporal sequences and long-term memory, which is relevant to the analysis of neural data (primarily graph-based). Neuronal representations are discussed in the following subsection. ResNet is widely used for training deep neural networks, and CNNs are well-suited for processing spatial data. Their ability to detect patterns and features in grid-like structures makes them suitable for analyzing two-dimensional or three-dimensional projections of neuronal morphologies. There are also other architectures, such as Recurrent Neural Network (RNN), Multilayer Perceptron (MLP), Visual Geometry



```
1 1 0 0 0 2.936 -1
2 1 -2.47 1.55 0 2.936 1
3 1 2.48 -1.55 0 2.936 1
4 7 -0.56 2.89 -0.5 0.575 1
5 7 -1.99 4.24 -0.5 0.575 4
6 7 -2.43 5.66 -0.5 0.575 5
7 7 -3.32 7.13 -0.5 0.575 6
8 7 -4.33 9.12 -0.5 0.575 7
```

Fig. 5. Some morphologies representations. (A) and (B) Image-based (Mata et al., 2019; Zhang et al., 2021), (C) Point-based (Zhang et al., 2021), (D) Graph-based (Cuntz et al., 2010), (E) Voxel-based (Lin and Zheng, 2018), and (F) Skeleton-based (Jiang et al., 2023).

Group (VGG), Deep Recurrent Neural Network (DRNN), Graph Neural Network (GNN), Fully Convolutional Neural Network (FCNN), and Kohonen Map.

The diversity of ANN methods and architectures reported in the literature underscores the need to investigate efficient and robust solutions for neuronal classification, reflecting this problem's relevance in neuroinformatics. Given that DL methods can handle raw data and/or feature-engineered data, and bearing in mind the data volume required by this approach, we further detail the morphological representations commonly used in machine-learning-based neuronal classification. For example, CNNs and their variants, such as ResNet and VGG, can analyze morphological data extracted from images, including three-dimensional neuronal reconstructions. Given the crucial role of morphological representation in determining the effectiveness of ML models, the following section examines the most commonly used approaches to encoding neuronal morphology. Understanding these representations is essential for selecting appropriate classification methods and optimizing model performance. Besides, in the discussion section, we provide an extensive analysis correlating classification methods with morphology representations and evaluation measures.

Morphologies representations

It is essential to rely on a robust representation of each neuron to compare neuronal morphologies and classify them accurately (Laturnus et al., 2020). In this sense, to address *RQ2: What kind of representation do the classification models work on?* We present the various forms of representing neuronal morphology for subsequent feature extraction and classification. We have the main neuronal representations displayed in Fig. 5. The very first representation used in neuron studies was the image 2D (Fig. 5(A)), recalling Ramon y Cajal's draws (Cajal, 1899). One alternative to the 2D image is the equivalent representation in points, which is still the gold standard of representation using SWC files (Fig. 5(C)). Constant advances in image acquisition methods and the processing of these images have enabled 3D representation (Fig. 5(B)), which now encompasses the notion of depth, along with volume and perceivability from all angles. This representation is instrumental for neuroscientists in visualizing neurons; few studies have used 3D representations to classify neuronal morphologies.

Graph-based representation (Fig. 5(D)) is similar to point-based but features structural dependency between points, based on a tree structure where the sum represents the root node. Voxel-representation (Fig. 5(E)) uses the concept of voxel, a unit of 3D space that represents a small cube in a 3D grid, usually used to divide the brain into discrete regions (used in the functional Magnetic Resonance Imaging (fMRI) or other volumetric imaging systems). It can also be used to represent neurons. Finally, the Skeleton-based concentrates on the structure of dendrites instead of volume (voxels), as can be seen in Fig. 5(F). We discuss each representation and its use below.

Image-based representation: image-based representation is the most prevalent, used in 13 studies (37%). This category refers to 2D or 3D images of neuronal morphology obtained using microscopy techniques such as confocal or fluorescence microscopy. For instance, in the work by Mata et al. (2019), images were acquired by photographing neurons labeled with Green Fluorescent Protein. In these cases, features can be directly extracted from the image, such as the shape of dendrites, the distribution of branches, *etc*. This finding is consistent with the growing use of deep learning algorithms, which can operate directly on raw data.

Point-based representation: This representation is the second most prevalent (approximately 22%). Neuron morphology is represented in the SWC file format, an acronym derived from the initials of EW Stockley, HV Wheal, and HM Cole (Stockley et al., 1993). NeuroMorpho.org uses this format to provide neuron data, in which each line in the SWC format contains seven values for a compartment: the general label and compartment type, the x, y, and z coordinates, the radii, and the connectivity link. Thus, the data is referred to as "unstructured" compared to image-based representations, which are "structured". Zhang et al. (2021) observed that this file format is challenging to analyze with traditional machine learning methods. It usually contains significant morphological errors that make it difficult to classify neuron types.

Graph-based representation: As the third most common representation form, the neuron's morphology is represented as a graph. Neurons have structures that resemble trees, a crucial characteristic for their biological functions (Cuntz et al., 2010). Consequently, we can model a neuron as a directed tree graph, with the root at the soma and directed edges connecting the nodes, forming the neuronal tree. This graph-based approach facilitates the visualization of complex neuronal connections and serves as a bridge to detailed graph-theory analysis (Sporns, 2018).

Skeleton-based representation: Unlike graph representation, skeletons are structures that capture the essence of neuronal morphology, typically reducing the neuron's complexity to a set of lines or traces representing the neuron's central structure or internal structural connectivity. According to Jiang et al. (2023), this representation can be used for quantitative analysis of neuronal cell structures, including the calculation of subcellular characteristics and neuron-type classification based on three-dimensional shapes.

Voxel-based representation: Lin and Zheng (2018) were the only researchers to report using a voxel-based representation. They employed a data transformation method that uses coordinate nodes and parent-compartment labels from the SWC format to generate three-dimensional information. This approach enables the construction of 3D voxel graphs of neurons and can be viewed as a dimensionality-reduction technique, as it reduces computational complexity.

Sequence-based representation: The topology of the neuronal tree is organized as a sequence of neurons' substructures. The sequential structure provides a natural representation of projection orders and enables the use of various Deep Sequential Models (Xiong et al., 2024).

Besides, spike train representations (i.e., patterns of neuronal firing recorded over time), microscopy videos, and patch-clamp recordings (a technique that provides detailed information on the electrical activity of a single cell) were used only once. We emphasize that image-based representation is a two-dimensional approach, in which morphological details are captured on discrete planes that can be stacked to generate a three-dimensional (3D) visualization. In contrast, the voxel-based representation is SWC format data transformed into 3D neuron voxel graphs (Lin and Zheng, 2018).

To deepen understanding of these results, we analyzed the features extracted (morphometrics, topological, electrophysiological and density maps) in studies using the aforementioned representations. Our found that **morphometric features** are the most are prevalent, being used in 30 studies (85%). In this approach, neuron morphology is characterized by morphometric properties, such as dendrite length, number of branches, and branching angles, among 150 other metrics listed by Leite et al. (2024). These characteristics can be quantified using methods such as Sholl analysis (Sholl, 1953), which assesses the spatial distribution of dendrites from the soma, or specialized software tools for this analysis, such as L-Measure (Scorcioni et al., 2008) and others (Leite et al., 2024). These features can be extracted from all forms of representation except patch-clamp recordings and microscopy videos.

Topological and electrophysiological features rank second, appearing in 5 studies (14%) each. Topological features encompass structural characteristics that describe the spatial organization and connectivity within neurons and neural networks. Electrophysiological features are the neurons' electrical properties, including parameters such as the resting potential and the duration of action potentials. Troullinou et al. (2021) established a new automated method for neuronal classification based on rodent neuronal activity, specifically utilizing raw Ca2+ signals. Similarly, Hiatt et al. (2022), Ophir et al. (2023), Barros et al. (2022), Ophir et al. (2024) also based their approaches on electrophysiological data.

Finally, **density maps** were used in only one study (Laturnus et al., 2020), which systematically compared them with other neuronal characteristics. According to the authors, density maps are one-dimensional or two-dimensional projections of neural morphology. These projections capture the spatial distribution of specific neuronal features, such as dendrite density. This diversity of approaches highlights the complexity and variety of information that can be leveraged for neuronal automated classification. We emphasize that the choice of representation will depend on the type of available data, the extracted features, and the specific needs of each study. The following section addresses the final research question regarding evaluation metrics.

Evaluation metrics

We present the metrics used to evaluate and validate the data from the studies in this Subsection, addressing *RQ3: How are the classification models evaluated?* We identified nine metrics, illustrated in Fig. 6. As expected, accuracy is the primary metric, used in 29 studies (83%). It assesses the proportion of correct predictions relative to the total predictions, providing a general indication of the model's ability to classify data correctly. Next, we observe the significant presence of the confusion matrix in 11 studies (31%). The confusion matrix enables detailed analysis of the model's performance by showing the distribution of correct and incorrect predictions across classes. Additionally, we highlight the Area Under the Curve, which is featured in 8 studies (23%) and used in classification model evaluation to measure the model's discriminative ability in distinguishing between positive and negative classes.

Other identified metrics include Precision, F1-Score, Recall, Sensitivity, Silhouette, and Specificity. These metrics are strategically selected to provide insights into different aspects of model performance. For example, metrics such as F1-score, Precision, and Recall provide a detailed analysis of accuracy in identifying positive and negative examples, accounting for potential class imbalance. Sensitivity and Specificity, on the other hand, assess the model's ability to correctly distinguish between positive and negative examples. Finally, the Silhouette metric is used to measure intra-cluster cohesion and inter-cluster separation in clustering techniques used for subsequent classification, providing insights into the quality of data group separation. Six studies (20%) employed Cross-validation (also known as k-fold cross-validation) in conjunction with performance metrics. This procedure enables evaluation of the model's generalization ability by iteratively splitting the data into training and testing sets. Thus, this variety of metrics offers a comprehensive view of classification model performance. The following subsection addresses the neuroscience tools employed in the analyzed studies.

It is important to note that the papers did not use a single dataset that could be considered a baseline, making it difficult to compare the studies reliably. This observation reflects the complexity of the subject, given the species studied, the brain region of interest, the cell types considered, and the representations, among other variables that directly affect the experiments and, consequently, the evaluation measures. Although the choice of these measures is a critical aspect of machine learning, as is the choice of models, this is still an open question for constructing more robust experimental guidelines. We identify a research gap in the need for more studies on the classification of neuronal morphologies *in silico* to provide sufficient evidence to develop an experimental guideline.

Neuroscience tools

It became evident that the studies employed specific tools from neuroscience, whether for tasks such as digital reconstruction of histological images of neurons, visualization, or feature extraction. Consequently, this subsection identifies these tools and their respective functions. All tools were considered at this stage, except those not exclusively developed for neuroscientific investigations, such as ImageJ,[10] a software intended for image processing across various fields. Therefore, the main tools identified in our study are shown in Fig. 7.

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[10] http://imagej.nih.gov

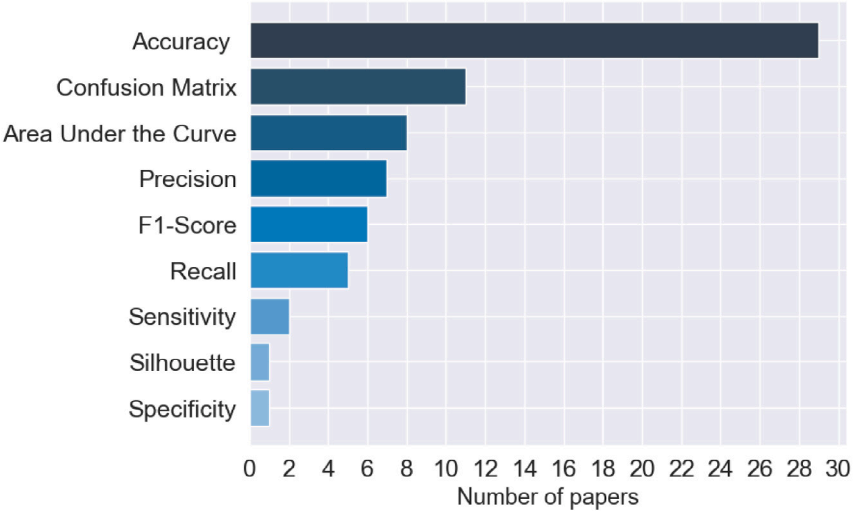

Fig. 6. Frequency of the evaluation measures used in the reviewed papers.

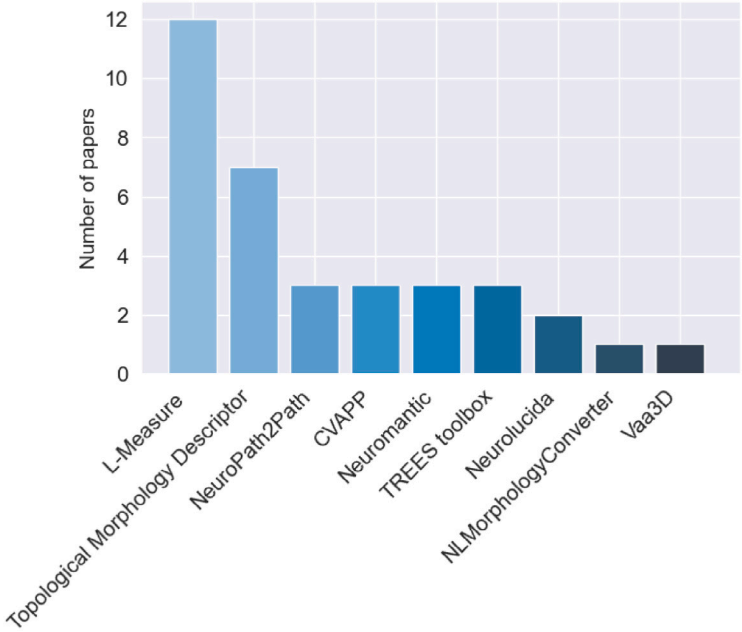

Fig. 7. Distribution of the main neuroscience tools used for feature extraction reported by the reviewed papers.

The L-Measure[11] stands out, being utilized by 12 studies (34%). This tool is a free and open-source software widely used in neuroscience for extracting 43 morphometric features from neuronal reconstruction files (Scorcioni et al., 2008). Examples of these metrics include neuronal width, height, and depth; number of branches and bifurcations; segment length; and fractal dimension, among others (Leite et al., 2024). In the same line of neuronal analysis, the Topological Morphology Descriptor (TMD) is prominent, used in 7 studies (20%) and NeuroPath2Path in 3 studies (8,5%). The TMD algorithm encodes the branching pattern of morphology, aiming to map the neuronal tree into a topological representation with less information loss compared to conventional morphometry (Kanari et al., 2018). On the other hand, NeuroPath2Path calculates the distance between two neurons and is compared to TMD in terms of its functionality (Batabyal et al., 2020). Alongside NeuroPath2Path, Neuromatic, and TREES toolbox is CVAPP. This tool is valuable for visualizing, editing, and converting files, offering a user-friendly interface that allows zooming, panning, and rotating neuronal reconstructions in Neurolucida, SWC, and 3D formats for detailed analysis (Cannon et al., 1998).

Tools for the digital reconstruction of neuronal morphologies are also prominent. Among these, Neuromantic is the most utilized software across studies, facilitating manual and semi-automatic reconstruction processes (Myatt et al., 2012). Neuromantic is highly intuitive for three-dimensional reconstructions and exports files in SWC format. Other tools offering similar functionality include the TREES toolbox (Cuntz et al., 2011), Neurolucida (Glaser and Glaser, 1990), shown in Fig. 9, NeuroMorpho.org[12] is the central database used in automatic neuron classification studies, with 19 studies (54%) included is the NLMorphologyConverter[13] that facilitates the conversion between 3D

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[11] http://cng.gmu.edu:8080/Lm/

[12] https://neuromorpho.org/

[13] http://neuronland.org/NL.html

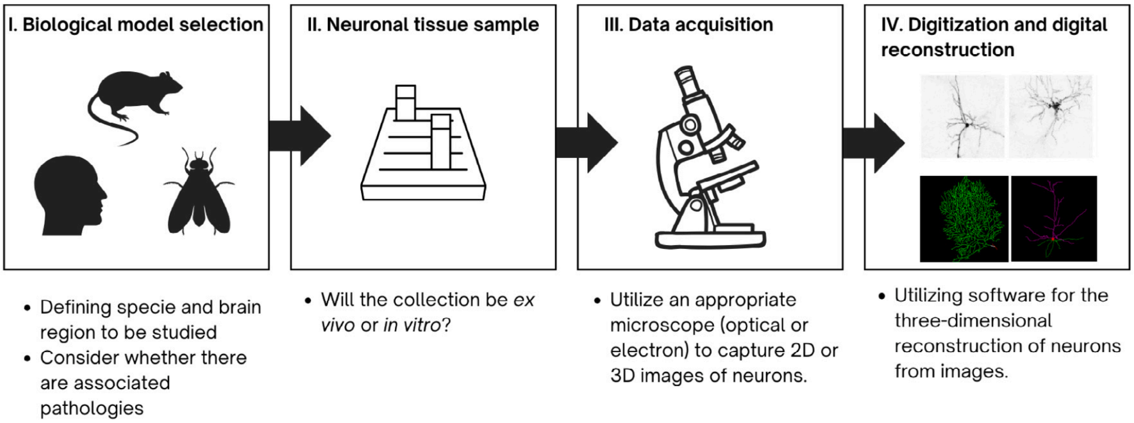

Fig. 8. Summary of the steps for acquiring neuronal morphologies. Images from Mata et al. (2019) and 3D reconstructions available at NeuroMorpho.org.

neuron morphology formats. In our review, it was utilized by Laturnus, Kobak, and Berens (Laturnus et al., 2020) to convert reconstructions saved in ASC format to SWC format.

Neuronal morphologies data sources

The usual process obtaining neuronal morphologies from samples this consists of the following steps (Fig. 8): (i) selection of a sample individual, which can vary in species, region of the brain, or even associated pathologies; (ii) separation of tissue from the individual (*ex vivo* or *in vitro*); (iii) preparation of slides for microscopy and data acquisition; (iv) digitization and reconstruction of the images into a digital representation scheme. Taking into account this critical step and its inherent diversity (e.g., conditions/diseases, species, brain areas), we summarized the primary data sources used in neuronal morphology classification.

As can be seen in Fig. 9, NeuroMorpho.org[14] stands out as the central database used in automatic neuron classification studies, covering 19 studies (54%) mapped in our systematic review. This repository was launched in 2007 (Ascoli et al., 2007), and in its current version 8.6.10 (last updated in 2024), has been contributed to by more than 900 laboratories around the world and contains 261,316 3D digital reconstructions of neurons and glial cells. An interesting point is that 9 studies (25%) use their own datasets, suggesting that researchers tend to create and use specific datasets. This may be because some of these studies acquire microscopy images of neurons for subsequent digital reconstruction and classification (Mata et al., 2019; Stojić et al., 2021b; Troullinou et al., 2021). Next, we identified that 5 studies (16%) also use databases created by third parties (Laturnus et al., 2020; López-Cabrera et al., 2020; Hiatt et al., 2022; Zhu et al., 2023; Jiang et al., 2023).

In addition to NeuroMorpho.org, other worldwide accessible data sources used are Allen Cell Types[15] and the Blue Brain Project.[16] The Allen Cell Types provides a vast dataset on different types of brain cells, including their electrical and morphological properties, derived from single-cell studies conducted in mice and humans (Hawrylycz et al., 2012). Nevertheless, the Blue Brain Project, led by the École Polytechnique Fédérale de Lausanne, aims to reconstruct and simulate the human brain at the cellular and synaptic levels, providing access to a wide range of data on neuronal structure and function (Markram, 2006). It is critical to note that NeuroMorpho.org is a broad repository that aggregates data from many species and sources, including Allen Cell Types. In contrast, the other initiatives are more specific: Allen Cell Types uses proprietary data from mouse and human subjects, whereas the Blue Brain Project focuses solely on the mouse brain. Recent databases, such as the Drosophila complete brain connectome released in 2022 (https://flywire.ai/) (Dorkenwald et al., 2022), could be helpful. These complementary resources enhance research in neuronal classification, providing researchers with access to diverse data for their investigations.

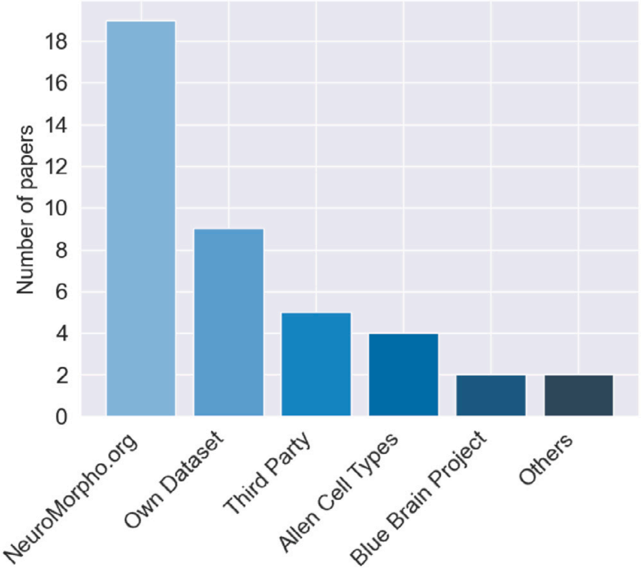

Fig. 9. Summary of the principal data sources for the neuronal reconstructions used in the papers analyzed.

To conclude, NeuroMorpho.org is the leading database of neuronal morphologies; however, with recent advances in neuroscience, the Allen Cell Types database also includes electrical properties alongside morphological ones. The Blue Brain Project focuses on human cells and also contemplates synaptic aspects. We emphasize that studies often draw on multiple data sources. For example, Chen et al. (2022) used data from Allen Cell Types, Brain Image Library, and Janelia MouseLight (the latter two have been grouped under "others" in Fig. 9). These research findings expand the body of knowledge by systematically mapping data sources used in *in silico* neuronal classification and by aggregating taxonomic information.

Categories of neurons

Classifying neurons based on their anatomical characteristics is so complex that it has led to a division in neuroscience between

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[14] https://neuromorpho.org/

[15] https://celltypes.brain-map.org/

[16] https://www.epfl.ch/research/domains/bluebrain/

Table 7
Terminology description of class, subclass, type, and subtype categories of neuron cells.

Terminology	Description
Class	It refers to a broad, primary category that groups neurons based on major morphological or functional characteristics.
Subclass	It refers to a subdivision within a class, usually based on genetic or molecular markers. For example, within the class of GABAergic interneurons, subclasses are defined by the expression of genes such as parvalbumin, vasoactive intestinal peptide, and somatostatin.
Type	It refers to a more refined classification that takes into account not only morphological characteristics but also electrophysiological properties, synaptic connectivity patterns between neurons, and genetic expression.
Subtype	It indicates a more specific level of differentiation, considering multiple combination criteria. For example, a subtype can be defined not only by morphology but also by specific location or functional behavior.

lumpers and splitters, analogous to the distinction in species classification (Simpson, 1945). The first tends to group neurons into broader categories, aiming to identify common characteristics that unite them into a single class. In contrast, the second approach categorizes neurons into more specific groups, recognizing individual differences among them and subdividing them into subclasses. In the current state of knowledge, we encounter four distinct terminologies that are commonly used: “class”, “subclass”, “type”, and “subtype” (Masland, 2004; Zeng, 2022; Ophir et al., 2024; Kanari et al., 2019). The reviewed papers fit this classification taxonomy; hence, our results reinforce evidence for these categories and corroborate the literature. The definitions of these terms are presented in Table 7, emphasizing the importance of a systematic approach to understanding the nervous system.

There are many approaches to categorizing cell types, since cell types in the brain and the body exhibit diverse properties in many modalities—molecular, morphological, physiological, and functional. Zeng (2022) argues that a transcriptomic cell type taxonomy must be linked to anatomical and functional information to evaluate the validity of the transcriptomic taxonomy and determine the appropriate level of granularity. Recent research findings by Shainer and colleagues (Shainer et al., 2025) indicate that transcriptionally similar neurons can diverge in shape, connectivity, and visual responses. Thus, extrinsic, position-dependent factors expand the phenotypic repertoire of genetically similar neurons. Regarding the subtypes, Di Bella and colleagues (Di Bella et al., 2024) add that neurosubtypes are also characterized by their molecular profiles, axonal extension, layer organization, and physiological properties. Thus, it is consistent with Zeng’s suggestion of developing a “tree of cell types” for an overarching classification of cell types and delineation of their origins and relationships. The following subsection delves deeper into discussions of neuronal taxonomy in the reviewed papers.

Neuronal taxonomy aspects

Several factors are crucial for obtaining comprehensive results in neuronal classification, including the choice of species or biological model, the specificity of the anatomical region within the brain, and the precise identification of the cell types involved. These elements not only delineate the characteristics of the research but also directly influence the understanding of neuronal processes and the applicability of the results. Figs. 10, 11, and 12 illustrate these aspects.

Fig. 10 shows ten species mapped in this review. The mouse and rat are the most prevalent models, covering 13 studies (37%). These rodents have been the typical model in neuroscience investigations over the years due to their similarity to the human nervous system and the availability of genetic tools and experimental resources (López-Cabrera et al., 2020; Xu et al., 2022). Moreover, it is straightforward to induce similar human pathologies in them, such as Parkinsonism, Alzheimer’s, Multiple Sclerosis, and other neurodegenerative diseases. This enables assessment of its impact on neuronal morphology, thereby building parallels and informing treatment in humans (Dawson et al., 2018). The usage of other species is also notable for the same reasons, such *Drosophila melanogaster*, *Caenorhabditis elegans*, wallabies, chimpanzee, monkeys, *Danio rerio* — known as zebrafish — and *Ciona intestinalis*, and, obviously, humans. These species offer specific advantages in nervous system complexity, experimental accessibility, or genetic diversity, thereby expanding the scope and applicability of research (Dawson et al., 2018). In this context, it is important to emphasize that the chosen species reflect the availability of connectome data.

Beyond species, delineating anatomical regions is crucial for understanding neuronal processes. Mapping anatomical regions remains an active area of research (Siddiqi et al., 2022; Yen et al., 2023). Identifying the relationship between brain areas and their functions, as well as intra- and interregional interactions, is a promising research field known as connectomics (Beyer et al., 2022). By way of illustration, connectomics is such a recent concept that it has not yet appeared in the search reports presented on Google Trends[17] at the time of this consultation. In this regard, there are international efforts to map the human connectome. For example, the Human Connectome Project (Van Essen et al., 2013), funded by the NIH Neuroscience Blueprint Institutes and Centers, has already led to scientific discoveries about the human cortex and individual differences in behavior. In addition, a Chinese initiative launched in 2017 aims to map the human connectome, thereby filling gaps in the field by providing imaging, behavioral, and genetic data (Ge et al., 2023). These projects are notable examples of how collaborative science and technological advances can advance research in neuroscience and related fields.

Fig. 11 shows that the neocortex attracts considerable research interest, possibly due to its role in higher cognitive functions such as sensory perception, cognition, and language (Turner et al., 2022). Besides, other factors include greater accessibility, its role in current debates on cell-type classification, and the scientific community’s interest in the structural characteristics of the mammalian neocortex (Zemke et al., 2023; Schneider-Mizell et al., 2025; Arkhipov et al., 2025; Weis et al., 2025). This brain region is characterized by a high neuronal density and is organized into six distinct layers, each contributing uniquely to its function (López-Cabrera et al., 2020). This intricate organization provides an exceptional framework for exploring key aspects of brain function, including neuronal connectivity, the synaptic plasticity mechanisms that underlie learning and memory, and the processing of sensory and motor information. The varied cellular architecture within the layers enhances our understanding of how the brain encodes and retrieves information, making the neocortex a fascinating subject for neuroscientific inquiry (Turner et al., 2022). It is essential to bear in mind the new advancements in data acquisition in neuroscience at all levels, such as molecular (e.g., genetic expression (Yuste et al., 2020)), cellular morphologies (e.g., morphological characterization), cellular physiology (e.g., mitochondrial behavior, electrical properties), and, finally, the functional aspects (e.g., emotion, vision, memory). However, they all center on neuronal morphology (phenotype), which is essential for understanding brain function, degenerative diseases, and aging, among other processes.

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[17] https://trends.google.com/trends/explore?date=now%201-d&q=connectomics&hl=en-GB *accessed on 27 Nov 2024.*

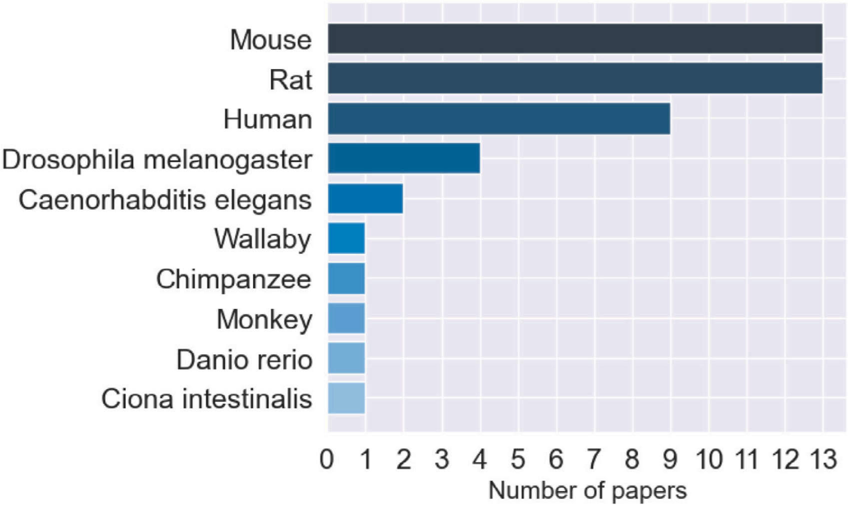

Fig. 10. Summary of the biological samples used in this research, categorized by animal species.

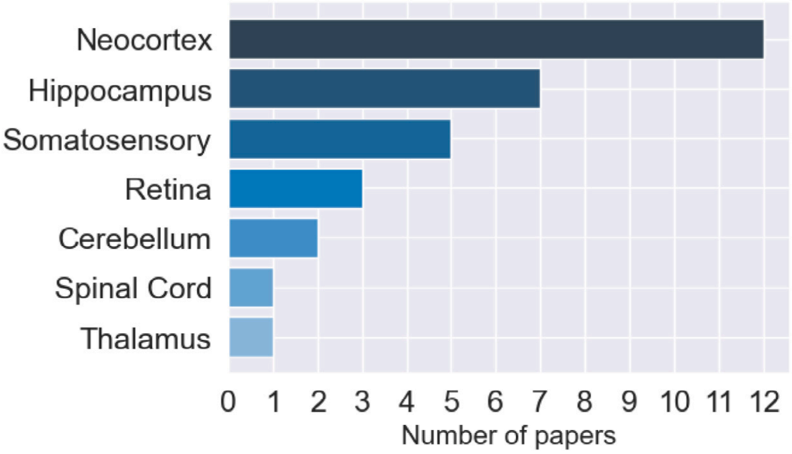

Fig. 11. Distribution of the neuronal morphologies according to the seven anatomical regions reported in the papers reviewed.

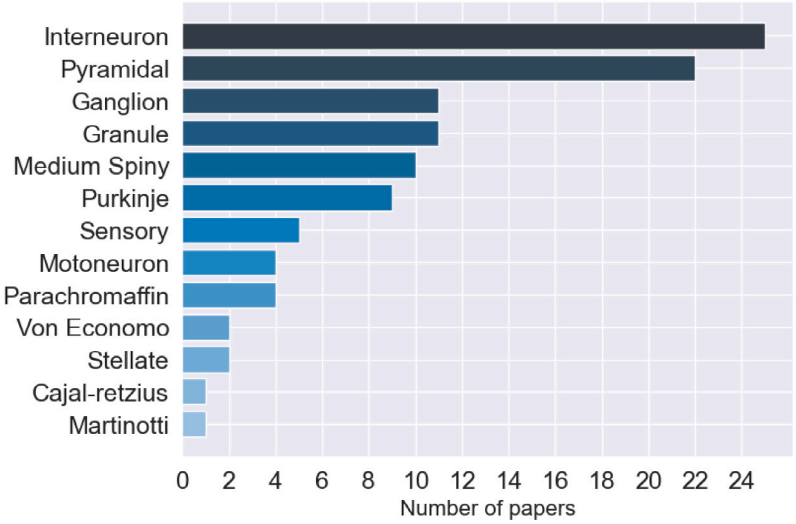

Fig. 12. Cells origin studied according to neuronal type.

On this account, understanding brain function is essential to identifying the most cell types in the region under scrutiny. Fig. 12 illustrates the main neuronal types for characterization and classification. In this study, we highlight the use of 13 neuronal types, with interneurons and pyramidal cells being predominantly used. This preference can be attributed to the fact that these are the two main types of neurons in the neocortex (Zeng and Sanes, 2017), the most-studied brain region due to its association with cognition and other complex functions, as shown in Fig. 11.

As shown in Fig. 12, in addition to these two predominant cellular types, various morphologies have been identified. Notable examples include ganglion, granule, and medium spiny neurons; Purkinje cells; sensory and motor neurons; Parachromaffin cells; Von Economo neurons; Stellate, Cajal-Retzius, and Martinotti cells. Each of these morphologies possesses unique characteristics in shape, synaptic connectivity, and function, contributing to the functional diversity of the nervous system and the complexity of neural circuits. At this point, we also analyzed the characteristics of the classification problems addressed in the papers, as shown in Table 8. Most involve multi-class classification problems (approximately 70%), which involve categorizing neurons into several distinct classes. In contrast, only three papers (8.5%) deal with binary classification. Additionally, we note that in seven papers (20%), it was not possible to clearly determine the type of classification problem due to insufficient information in the methods described.

Another relevant aspect is that neurons can be classified into types, such as basket cells, amacrine cells, GABAergic cells, nitrergic cells, cholinergic cells, and glutamatergic cells, which belong to the interneuron class. The choice of the number of classes and types is related to the research problem's specificity and the availability of detailed data on different neuronal types. Table 9 summarizes the research findings discussed above. In the first column, we present the paper selected based on the inclusion/exclusion criteria and quality assessment, the identified data source, and the species, brain regions, and cell classes used in their experiments for *in silico* neuronal morphology classification.

As discussed in Section "Neuronal morphologies data sources", microscopy techniques are essential for digitizing and reconstructing images. Thus, the morphology of a cell can be reconstructed from high-resolution light microscopy datasets, which may be enhanced with colorimetric or fluorescent sparse labeling, or from electron microscopy datasets. However, it is important to recognize that significant differences arise between neurons reconstructed using electron and optical microscopes due to differences in resolution. These discrepancies can lead to noticeable differences in the research subjects, methodologies, and objectives across morphological studies.

We also found that many studies do not specify the microscopy technique used for digital reconstructions. Instead, they generally refer to these reconstructions in a vague manner or simply mention data sourced from the NeuroMorpho.org repository (Batabyal et al., 2020; Troullinou et al., 2021; Kirch and Gollo, 2020; Grbatinić et al., 2018; Friedman, 2020). In some instances, reconstructions were performed using electron microscopy (Laturnus et al., 2020; Jiang et al., 2023; Liao et al., 2024), while others were based on optical microscopy imaging (Lin and Zheng, 2019; Stojić et al., 2021b; Hiatt et al., 2022), including fluorescent microscopy (Mata et al., 2019).

Despite not having explicit research questions associated with this data in the systematic review protocol, we provide the information presented in Table 9 to contribute to the body of knowledge with a *bird-eye* view regarding a crucial aspect of data classification: data quality. There is consensus in machine learning research that high-quality inputs are crucial for building reliable models. Trustworthy artificial intelligence relies on curated data to such an extent that data analysis methodologies and frameworks encompass the understanding of data, such as the Cross-Industry Standard Process for Data Mining (CRISP-DM) (Wirth and Hipp, 2000) and the Data Science Trajectories (DST) (Martínez-Plumed et al., 2019).

Table 8
Classification overview per study, containing the number of classes and types.

Reference	How many classes/types of neurons?	What type of classification problems?
Batabyal et al. (2020)	5 Classes	Multi-class
Grbatinić et al. (2018)	1 Class, 2 types	Binary
Kanari et al. (2019)	1 Class, 17 types	Multi-class
Kirch and Gollo (2020)	6 Classes	Multi-class
Laturnus et al. (2020)	1 Class, 11 types	Multi-class
Lin and Zheng (2018)	1 Class, 4 types	Multi-class
Lin and Zheng (2019)	2 Classes, 1 type	Multi-class
Lin et al. (2018)	9 Classes, 8 types	Multi-class
Lopez-Cabrera and Lorenzo-Ginori (2018)	2 Classes	Binary
López-Cabrera et al. (2020)	2 Classes	Binary
Mata et al. (2019)	Not Described	Not Described
Peach et al. (2021)	2 Classes	Multi-class
Stojić et al. (2021b)	1 Class, 3 types	Multi-class
Troullinou et al. (2021)	2 Classes	Multi-class
Khalil et al. (2022)	7 Classes	Multi-class
Barros et al. (2022)	Not Described	Not Described
Yang et al. (2021)	Not Described	Not Described
Zhao et al. (2022)	5 Classes	Multi-class
Hiatt et al. (2022)	Not Described	Not Described
Chen et al. (2022)	2 Classes	Multi-class
Friedman (2020)	1 Class, 1 type	Not Described
Zhu et al. (2023)	3 Classes, 4 types	Multi-class
He et al. (2023)	7 Classes, 3 types	Multi-class
He et al. (2022)	8 Classes, 3 types	Multi-class
Wei et al. (2023)	8 Classes, 3 types	Multi-class
Zheng and Lin (2019)	6 Classes, 5 types	Multi-class
Xiong et al. (2024)	Not Described	Not Described
Jiang et al. (2023)	6 Classes, 1 type	Multi-class
Zhang et al. (2021)	8 Classes, 3 types	Multi-class
Ophir et al. (2023)	1 Class, 2 types	Multi-class
Sun and Zhao (2024)	5 Classes, 2 types	Multi-class
Ophir et al. (2024)	1 Class, 2 types	Multi-class
Liao et al. (2024)	Not Described	Not Described
He et al. (2024)	2 Classes	Multi-class
Kanari et al. (2024)	2 Classes	Multi-class

Discussion

Neuronal classification has been a challenging topic for over a century (Cajal, 1899). Many efforts are still needed to establish a taxonomy of neuronal morphologies, given the diversity of neuronal types and the lack of consensus in their definitions and nomenclatures (DeFelipe et al., 2013; Zeng, 2022; Domcke and Shendure, 2023). Our study contributes to the body of knowledge by synthesizing key aspects of automated neuronal morphologies classification, including the terminology commonly used in neuroscience, the main Machine Learning algorithms and ANN architectures, the types of morphological representations, the feature extraction methods, and the evaluation metrics used in this context. The results reinforce the crucial role of the NeuroMorpho.org database in the neuroscientific community. Since its launch 17 years ago, this database has continuously accumulated a vast body of detailed data on neuronal morphology, thereby promoting collaboration among scientists and enhancing the replicability and transparency of research. Approximately 25% of studies use their own datasets, which may introduce bias into the results, as these datasets may reflect researchers' specific areas of interest or expertise and may not adequately represent neuronal diversity.

Most papers focus on classifying general neuronal classes rather than more specific types. This trend suggests a preference for characterizing and distinguishing broad neuronal categories, which can be attributed to the greater availability of data on general classes and their relevance to practical and theoretical applications. Although studies have focused on classifying neuronal types (Grbatinić et al., 2018; Kanari et al., 2019; Laturnus et al., 2020; Lin and Zheng, 2018;

Table 9
Studies summarization, containing data source, species, brain regions, and cell-classes per work.

Ref.	Data source	Species	Brain regions	Cell-classes
Batabyal et al. (2020)	NeuroMorpho	Mouse	Neocortex, Hippocampus	Pyramidal, Ganglion, Granule, Motoneuron, Purkinje
Grbatinić et al. (2018)	Own Dataset	Human	Neostriate Nuclei	Interneuron
Kanari et al. (2019)	Own Dataset	Rat	Somatosensory	Pyramidal
Kirch and Gollo (2020)	NeuroMorpho	Mouse, Human, Rat, Wallaby, *Drosophila melanogaster*, Monkey	Neocortex, Hippocampus, Cerebellum, Forebarin, Retina, Anterior Cingulate	Pyramidal, Purkinje, Ganglion, Sensory, Granule, Interneuron
Laturnus et al. (2020)	Third Party	Mouse	Retina, Neocortex	Interneuron
Lin and Zheng (2018)	NeuroMorpho	*Drosophila melanogaster*	Not Described	Interneuron
Lin and Zheng (2019)	NeuroMorpho	*Caenorhabditis elegans*, Zebrafish	Not Described	Interneuron, Motoneuron
Lin et al. (2018)	NeuroMorpho	Human	Not Described	Cajal-Retzius, Interneuron, Von Economo, Stellate, Medium Spiny, Sensory, Pyramidal, Granule, Ganglion
Lopez-Cabrera and Lorenzo-Ginori (2018)	NeuroMorpho	Mouse	Neocortex	Interneuron, Pyramidal
López-Cabrera et al. (2020)	NeuroMorpho, Third Party	Mouse	Neocortex	Interneuron, Pyramidal
Mata et al. (2019)	Own Dataset	Rat	Hippocampus	Not Described
Peach et al. (2021)	Blue Brain Project	Rat	Somatosensory	Pyramidal, Interneuron
Stojić et al. (2021b)	Own Dataset	Human	Principal Olivary Nucleus	Interneuron
Troullinou et al. (2021)	Own Dataset	Mouse	Hippocampus	Pyramidal, Interneuron
Khalil et al. (2022)	NeuroMorpho	Human, Mouse, Rat	Hippocampus, Retina, Spinal Cord, Somatosensory, Motor	Ganglion, Pyramidal, Medium Spiny, Martinotti, Interneuron, Purkinje, Granule
Barros et al. (2022)	Blue Brain Project	Rat	Somatosensory	Not Described
Yang et al. (2021)	Allen Cell Types	Mouse	Not Described	Not Described
Zhao et al. (2022)	NeuroMorpho	Not Described	Hippocampus, Neocortex, Basal Ganglia, Somatosensory, Cerebellum	Granule, Ganglion, Purkinje, Pyramidal, Medium Spiny
Hiatt et al. (2022)	Third Party	*Drosophila melanogaster*	Not Described	Not Described
Chen et al. (2022)	Brain Image Library, Janelia Mouselight, Allen Cell	Not Described	Not Described	Pyramidal, Interneuron
Friedman (2020)	NeuroMorpho	Rat	Neocortex	Interneuron
Zhu et al. (2023)	NeuroMorpho, Third Party	Mouse	Not Described	Medium Spiny, Stellate, Pyramidal
He et al. (2023)	NeuroMorpho	Rat	Not Described	Interneuron, Pyramidal, Ganglion, Granule, Medium Spiny, Parachromaffin, Purkinje
He et al. (2022)	NeuroMorpho	Not Described	Not Described	Pyramidal, Interneuron, Sensory, Ganglion, Purkinje, Granule, Medium Spiny, Parachromaffin
Wei et al. (2023)	NeuroMorpho	Rat	Not Described	Pyramidal, Interneuron, Sensory, Ganglion, Purkinje, Granule, Medium Spiny, Parachromaffin

(continued on next page)

Table 9 (*continued*).

Ref.	Data source	Species	Brain regions	Cell-classes
Zheng and Lin (2019)	NeuroMorpho	Not Described	Not Described	Von Economo, Interneuron, Motoneuron, Purkinje, Pyramidal, Sensory
Xiong et al. (2024)	Own Dataset	Not Described	Neocortex, Thalamus, Midbrain, Hypothalamus, Hindbrain, Cerebral Nuclei	Not Described
Jiang et al. (2023)	NeuroMorpho, Third Party	*Ciona Intestinalis*, *Caenorhabditis elegans*, Human, Rat, Mouse	Not Described	Pyramidal, Ganglion, Granule, Medium Spiny, Motoneuron, Interneuron
Zhang et al. (2021)	NeuroMorpho, Own Dataset	Rat	Neocortex	Ganglion, Granule, Medium Spiny, Parachromaffin, Purkinje, Pyramidal, Interneuron
Ophir et al. (2023)	Allen Cell Types	Mouse	Neocortex	Interneuron
Ophir et al. (2024)	Allen Cell Types	Human, Mouse	Neocortex	Interneuron
Sun and Zhao (2024)	NeuroMorpho	Chimpanzee, Rat, Mouse, Human	Neocortex, Hippocampus	Pyramidal, Granule, Medium Spiny, Ganglion, Interneuron
Liao et al. (2024)	Own Dataset	*Drosophila melanogaster*, Human	Not Described	Not Described
He et al. (2024)	NeuroMorpho	Rat	Not Described	Pyramidal, Interneuron
Kanari et al. (2024)	Own Dataset	Not Described	Not Described	Pyramidal, Interneuron

Ophir et al., 2023), they remain less prevalent and may face additional challenges due to the need for more detailed data. A relevant observation is that TMD, NeuroPath2Path, and TreeMoCo are tools that were evaluated in studies (Kanari et al., 2019; Batabyal et al., 2020; Chen et al., 2022). These tools emphasize the effort toward technological innovation in neuronal morphology classification. Understanding these tools and their applications provides a solid foundation for future research, enabling different research groups to utilize, refine, or draw inspiration from them to develop new methodologies or expand the scope of neuromorphological analyses.

The main finding was that modern classification and categorization methods employ machine learning techniques based on cellular morphological-structure data. The classifiers used performed well in the studies, emphasizing advances in the neuroscience community. Artificial neural networks were not widely recognized in neuroscience 19 years ago (Armañanzas and Ascoli, 2015). To provide a detailed analysis of the associations between Machine Learning methods and the most commonly used types of neuronal morphology representations, we constructed a co-occurrence graph, highlighting the predominant approaches in neuronal classification, as shown in Fig. 13. We observe that neural networks, particularly CNNs, are widely used to analyze morphologies represented as images. This preference stems from the demonstrated ability of CNNs to process and extract relevant features from visual data (Sun and Zhao, 2024; Kanari et al., 2024). On the other hand, SVMs have been frequently employed in graph-based and image-based representations. This trend can be attributed to the strong performance of SVMs in classifying structured, multidimensional data (Batabyal et al., 2020; López-Cabrera et al., 2020; Mata et al., 2019).

Moreover, image-based representations are the most widely used, as described in the "Morphologies representations" section. However, point-based representations are the most versatile, as they can be combined with a wide range of ML methods, including SVM, ANN, Decision Trees, K-Nearest Neighbors, Naïve Bayes, K-Means, XGBoost, Random Forest, and Logistic Regression. This suggests that point-based representations offer significant flexibility, enabling their application across different contexts and algorithms. Similarly, graph-based representations support multiple algorithms, highlighting their importance in scenarios where topological and structural relationships play a key role (Khalil et al., 2022). In contrast, more specific representations, such as spike trains, microscopy recordings, and patch-clamp recordings, are less common. Despite this, these representations play an important role in integrating morphological data with electrophysiological and dynamic information, broadening the scope of possible analyses (Hiatt et al., 2022; Ophir et al., 2024; Kanari et al., 2024). This integration represents promising potential for future applications, particularly for investigating complex neuronal functions.

The graph presented in Fig. 13 not only reinforces the role of Neural Networks and SVMs as popular strategies but also highlights the diversity of approaches that can be combined with different types of representations. This diversity reflects the complexity of neural classification problems and the need to align the ML method with the data's intrinsic characteristics to maximize the reliability of the analysis. Regarding research replicability, only 13 papers (37%) provide the source code. This is particularly significant since the availability of source code is essential for promoting the replicability and validation of scientific results. Furthermore, based on these papers, it was observed that the programming languages commonly used are Python, present in ten papers (Laturnus et al., 2020; Peach et al., 2021; Yang et al., 2021; Xiong et al., 2024; Jiang et al., 2023; Zhang et al., 2021; Chen et al., 2022; Ophir et al., 2024; Liao et al., 2024; Kanari et al., 2024), and Matlab, in three (Batabyal et al., 2020; Kirch and Gollo, 2020; Khalil et al., 2022). Both languages are known for their versatility and efficiency in scientific and computational analysis, reinforcing their popularity in neuroscience.

The Open Science era emphasizes collaboration and transparency in research, yet these practices still face significant challenges (Singh et al., 2021). One issue highlighted in our research is the limited sharing of scripts/code, which makes replicating and verifying results difficult and leads to significant time spent trying to understand and reproduce other researchers' methods rather than focusing on the principles underlying the experiments.

Research limitations

Some limitations must be acknowledged. It is inherent in the systematic process of selecting specific databases for study collection. Overall, we chose databases widely used for publishing scientific papers, assuming they would contain the highest number of relevant studies. Additionally, a limitation arose during the data extraction stage. Some

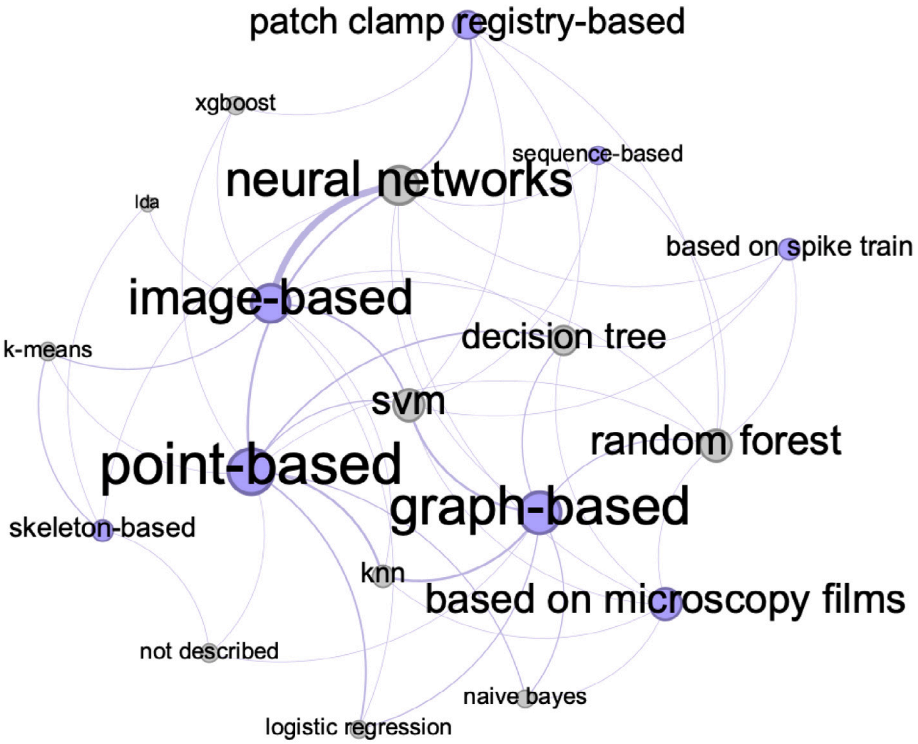

Fig. 13. Graph of co-occurrences of Machine Learning methods (gray) and morphologies representations (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

studies omitted essential aspects in their methodologies, such as the classification model adopted, specifying Neural Networks, describing types of neuronal morphologies, and the region of neuronal origin (e.g., neocortex, hippocampus, *etc.*). In these cases, we have noted as “Not Described” or “Not Used” the absence of this information, which has therefore not been taken into account.

In addition, we have observed limitations of *in silico* studies, including the lack of a standard dataset, which makes it difficult to compare studies. This is because variability across species, brain regions, cell types, and their representations directly influences experiments and evaluations. However, this limitation has a negative impact on reaching a consensus in defining a taxonomy for classifying neuronal morphologies.

Lessons learned and future directions

- There are far more publications in journals than conferences, far from the usual computer science proportion (one journal for three conferences). Although existing relevant conferences in computer vision intersect with *in silico* neuronal classification, there is a trend toward maintaining journals as outlets in this area, given its interdisciplinarity.
- In neuroscience, the primary animal models are rodents, with rats and mice together accounting for more than 70% of studies. This predominance underscores the relevance of these animals in research on nervous system function, owing to their ease of handling, high reproducibility, and significant biological similarities to humans. Besides, the neocortex is the brain region that attracts the most research interest due to its involvement in higher cognitive functions. The greater focus on the neocortex than on the hippocampus (which is more commonly studied in memory research) suggests that researchers emphasize brain areas associated with widely distributed and complex functions. These functions are directly associated with environmental interaction and the development of advanced concepts. Furthermore, this emphasis corresponds with an emerging research area, connectomics, which aims to map the brain’s neural networks to enhance our understanding of the structural and functional organization of the neocortex;
- There is a noticeable use of image-based neural representations, which is consistent with the increasing use of deep learning-based methods, given their ability to process raw data directly, thereby eliminating the need for feature engineering. Considering that NeuroMorpho.org only provides data in SWC (point-based representation) files, and the increasingly intensive use of some deep learning methods that receive images as input. As a future direction, we perceived a need to update the databases to allow them to store images and multiple representations in order to meet recent advances in analysis and classification techniques;
- Although the growing use of image-based representation, it is noteworthy to mention that deep learning-based methods work well with point-based or graph-based representations, considering their temporal/positional dependency characteristics. This reinforces the importance of different neural representations for neuronal morphology classification studies. Furthermore, some studies employed dimensionality-reduction strategies, such as voxel-based representations, to mitigate computational complexity. This may be a viable option for research groups with limited computational resources.
- Deep learning methods have significant future potential due to their reduced reliance on manual engineering and their ability to leverage computational resources and available data. However, in neuroscience, the limited availability of data — stemming from the diversity of research areas, including different species, brain regions, and cell types — hinders the widespread adoption of these methods. To address this challenge in the near future, it is essential to invest in data acquisition and to strengthen international initiatives such as the Human Brain Project, BRAIN initiative, and NeuroMorpho.org, as these can help overcome existing limitations;

- There is no single "best" method for classifying neuron morphologies. Furthermore, there is no clear consensus on the most appropriate evaluation measure, given the diversity of studies. The effectiveness of each approach and the evaluation measures adopted depend on multiple factors, including the type of neuron and the morphology representation, among other characteristics under analysis. A clear justification of evaluation measures and the correlation between the models and neuronal representations is desired in future works.
- As stated by Richards et al. (2019), recent advances in artificial neural networks can drive theoretical and experimental progress in neuroscience. While new convolutional neural network architectures enable image analysis without feature engineering, benefiting fields such as neuron classification, these artificial architectures facilitate comparisons and understanding of brain function and cognition.

Conclusions

This systematic review provided a comprehensive analysis of the neuronal morphologies classification panorama, shedding light on trends, gaps, and opportunities for future research. Our findings indicate that Deep Learning-based approaches have become popular, often leveraging automatic extraction of morphometric features from image-based representations. However, although Neural Networks have established themselves as the predominant method for classifying neurons based on their anatomical features, no single approach is universally superior. The effectiveness of each method depends on several factors, including the neuronal type, the morphological representation used, and the specific characteristics analyzed. In addition to the methodological aspects, we presented other insights summarized in Section "Lessons learned and future directions". We followed open science principles and made supplementary material available on https://github.com/fabiolobato/in_silico_neuronal_classification.

Based on our findings, this review can significantly advance neuroscience by providing a solid foundation for future research and by developing a robust taxonomy, which remains an important gap in the literature. Future research should focus on developing more replicable experimental frameworks that capture diversity and on exploring new learning paradigms, such as semi-supervised approaches, to address the relative sparsity of data. It is also clear that efforts are needed to develop more efficient and standardized data representations, culminating in the construction of databases that support multiple formats and representations, thereby providing greater experimental flexibility. Moreover, it is essential to evaluate additional metrics to provide a more comprehensive view of the model's performance. This should account for intrinsic characteristics of the experiments, such as class imbalance and robustness evaluation under noise addition, among others. Always bear in mind the human-in-the-loop paradigm to maintain the reliability of the research findings.

Given the above, the classification of neuronal morphologies remains a complex, multidisciplinary challenge that requires the joint efforts of specialists in neuroscience, data science, artificial intelligence, and related fields. The future of research in this field depends on the availability of standardized and diverse datasets, the continuous improvement of algorithms that have already demonstrated strong performance, and, perhaps most importantly, the strengthening of interdisciplinary collaboration. Besides, as new technologies emerge, their integration becomes of the utmost importance. The combination of transcriptomic, electrophysiological, and morphological properties obtained via Patch-seq, using a data-driven approach (e.g., machine learning and graph-based methods), can reveal the underlying mechanisms of brain function. Thus, this synergy is expected to drive significant advances in understanding the structure and function of the nervous system, paving the way for innovative applications in neuroscience and related areas. After all, we need to unravel the shapes of thoughts.

CRediT authorship contribution statement

Fábio Lobato: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jéssica Leite:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Antonio Jacob:** Validation, Supervision, Project administration, Funding acquisition. **Roberto Santana:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

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Declaration of competing interest

All authors declare that they have no competing interests.

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