

Towards a pragmatic definition of cell type

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Introduction

One of the basic classes in any undergraduate major in life sciences is the histology class. The students are tasked with identifying cell types across various tissues, looking for color and shape patterns in hematoxylin-eosin stains. The text-books, such as the one by Junqueira & Carneiro[???], work as manuals (in the Kuhnian sense)[1] that perpetuate the paradigms of what we know about a couple hundred cell types.

The concept of “cell type”, thus, is still based on century-old histochemical techniques - such as the Golgi-stains of neurons immortalized by Ramon y Cajal[2]. The histological influence is noticeable even in names given to cell types: “erythrocytes”, “eosinophil”, “basophils”, “oxyphilic cell of the thyroid”. The concepts we use are drawn from studies of microanatomy. The connection with anatomy leads to thinking about cell types as anatomical entities as if they were clearly dissectable and fixed in an organism. This may be the reason why attempts to quantify cell types use the scale of “hundreds” of human cell types [3] [4] [5].

New techniques have challenged this anatomy based conceptualization. From flow cytometry to patch clamping, to single-cell RNA-seq, we saw a burst of new categories, and novel cell “subtypes” and “families” popped up in the literature. The bursting intensified in the past few years, with the rise of projects to characterize *all* human cell types, like the Human Cell Atlas and HUBMAP [6] [???].

The advances in biology require us to find better answers for how to define a cell type. The concept might not have a “true” meaning, in a philosophical-realistic sense, but we can avoid the notion of natural cell types - “one presumed to exist in nature, which has a reality independent of its investigation” [7] - and strive to find nominal, pragmatic definitions for the pragmatic challenges of large scale biology. Otherwise, how can we precisely label single-cell data? How can we formalize the discovery of new cell types? How can we integrate the knowledge from the millions of scientific articles published every year?

The need for conceptual advance is perceived by the community [???] [8] [9] [10] [11] [12] [13], and new perspectives are arising. One core line of thought is evolutionary: the cell type as an evolutionary unit defined by a Core Regulatory Complex (CoRC) of transcription factors. That definition enables the drawing of parallels between the evolution of other biological entities (such as genes, proteins and species) to the evolution of cell types. Models of how multicellular life works greatly benefit from concepts such as “sister types” (cell types that diverged from a single ancestor), “cell type homology,” (cell types in different species that share a common evolutionary origin) and “cell type convergence” (cell types that execute similar functions, but which are not directly evolutionarily related). [???] [14]

However, as much as different concepts of species coexist [15], our quest to define cell types may take various forms. The challenge of representing cell types in the context of evolution is conceptually different from the challenge of representing cell types in biomedical experimentation. In that second direction, the groundwork of the Cell Ontology [16] [17] [18] project and the International Workshop on Cells in Experimental Life Sciences[19] [20] are notable. Their contributions base much of the views here and will be discussed in detail throughout the article.

The conceptual quest addressed by this work is one of the research synthesis and is summarized in the following question: which definition of cell type optimizes the rigorous description biomedical experiments?

We chose to use the term “cell type” to emphasize the focus on types as classes (or “kinds”) in contrast to real-world objects. The notion of “cell state” is used both to describe classes (e.g. activated T-cell) as well as for real world observations (e.g. the current state of a specific cell). One can argue that 2 cells can never be in the same state, in an extension of to the Heraclitian idea of not being able to step twice in the same river [21]. Other similar notions, such as a “cell set”, “cell population” and “cell cluster” can also reminisce of a specific, countable group of cells, frequently from a same experiment. The term “cell type” is used for relatively invariant classes of cells, with common characteristics.

The term “cell class” is also used in the literature, and would be a suitable synonym for our notion of cell type, as the main goal here is to refine the human-based theoretical classes. Classes that we can *instantiate*, i.e. assign to an observation of any real cell, in the same way we assign the class *Homo sapiens* to each and every human. The term “cell identity” has also been suggested for avoiding the cell type/cell state dilemma [22]. The notion of identity is however slightly different of the idea of class. We nevertheless opted to frame our work around “cell type” due to its historical usage and familiarity for the life sciences community.

For that goal, the body of the article is divided in 4 parts. In Part 1, we will bring a proposal of a set of rules that are sufficient for defining cell types. In Part 2, we will propose a small set of names for differentiating main classes of cell types. In Part 3, we will address the logical consequences of the proposed definitions. And in Part 4, we will discuss the pragmatic challenges for employing such definitions.

A set of 3 + 1 rules for defining a cell type

In an opinion article published in Cell Systems in 2017, researchers presented their views on the “Conceptual Definition of ‘Cell Type’ in the Context of a Mature Organism?” [???]. The opinions vary, and do not converge to a consensus. Many of the scientists see a core role of cells’ functions in defining cell types, a slippery road, as the meaning of “function” in biology is elusive [23].

Our pragmatic definition of cell type (for eukaryotic, multicellular organisms) consists of 3 + 1 simple rules. A cell type is a class of cells that *must* be:

- Explicitly defined
- Theoretically useful
- Identifiable for a defined taxon

And that *should* be:

- Hierarchically related to other cell types

For that specification, *must* represents an “an absolute requirement” and *should* represents that “there may exist valid reasons in particular circumstances to ignore a particular item” (as per RFC 2119 [24]).

For rule 1, by “explicitly defined”, we mean that the cell type needs to be followed by a clear definition, that would allow rational judgements of whether a singular cell belongs or not to the type. The definition *should* be *complete*, providing the necessary and sufficient criteria for classification. An example is a cell type defined by “expression of the proteins CD3 and CD4, but lacking CD8.” Even though there is still some ambiguity in that definition (see [25] [26] for longer discussions), it already states clear, reasonable criteria. Any combination of markers (or lack thereof) can define a different *cell type*. This extends to *any* definition, and small differences are enough for constituting new cell types. The degree of rigorousness cannot be decided a priori, as we still do not have a rigorous

framework for representing biological knowledge, but we *should* strive to make definitions as rigorous as possible. Other examples of what could be explicit definitions:

- A “big cell”, defined a class of cells with a length of more than 50 micrometers on any axis.
- A “human cortical neuron” is any cell in a human cortex that is able of producing an action potential.
- A “leukocyte” is a class of achromatic cells found in animal blood.

The recognition of multiple valid types of rules is not new. The first Cell Ontology article, in 2005, explicitly acknowledged criteria based on function, histology, lineage and ploidy.[16]. These features were combined in the definitions of “species-neutral” cell types[18], arguably useful for integrating databases, or for teaching biology. Gradually, we are acknowledging that we might need more specific classes to characterize experimental biology, leading to definition of species-specific types defined by granular characteristics. [27] [17].

As an analogy, when describing a new species, besides preserving a type specimen, a taxonomist must cover the species *diagnosis* - the ways one can tell a species from others. Even though there are standards for format, the taxonomy codes for botanics and zoology do not restrain which characters should be used, as there is a huge diversity of organisms.[28] In the same way, it might be unrealistic to restrict definitions of cell types to a single class of characters, like expression markers.

Rule number 2 is, thus, an explicit criteria that *must* be followed when talking about cell types scientifically: we need to define the taxons for which a given cell type is expected to manifest. The cell type, then needs to be findable in any individual of the taxon (or taxons) of interest, given the appropriate conditions (e.g. stage of life and biological sex). The set of taxons covered by a cell type is called here a *taxonomy scope* (or just *scope*) of the cell type. Note that, as cell types can be defined by function, and functions can converge, the taxonomix scope is not restricted to monophyletic taxa (“clades”). The definition of taxon used here is liberal, as any class of organisms that any researcher identify explicitly as a unit.

Knowing the scope is important to avoid the pitfalls of extrapolation. One recurrent extrapolation is that theories corroborated by mouse experiments are valid for human cells. This extrapolation is an instance of the classic problem of induction, detailed thoroughly in the Logic of Scientific Discovery. A specification of the scope a researcher is referring to would make inductive claims explicit and enable proper evaluation of claims. It is not safe to assume that a “mouse neutrophil” is simply a “neutrophil” that happens to be in a “mouse”. A definition of scope is essential to tease apart general claims from study-specific claims.

Rule number 3 is a rule of practical concern. There is a massive amount of “explicit definitions” that one scientist might come up with, due to the combinatorial nature of classes, far outnumbering the reported number of atoms in the observable universe. For that reason, a criterion of usefulness is necessary for deciding when a class of cells is considered a cell type. The simplest criteria of usefulness is one based on the individual: a valid cell type is whatever class any individual rationally finds useful.

Rule number 4 is one practical extension of the “usefulness” rule: a cell type has to be hierarchically anchored to other cell types for increased usefulness. Which means that a definition of a cell class is (for research synthesis concerns) of lower usefulness if it can’t be considered a “subclass” of other cell type. For our practical concerns, all imaginable cell types are subclasses of “cell of eukaryotes”. This is presented as a recommendation instead of a requirement as, in practice, it might be an overhead not strictly necessary for claims of discovery of new cell types and similar tasks.

The ontological organization is important for integrating knowledge across studies. A “transcriptomically-defined” cell type and a “electrophysiologically-defined” cell type are not the same, but they can be grouped in a “superclass” that contains cells that match either one or the other criteria. Practically, when describing a cell type, one should make an effort to insert it into the universe of interrelated cell types, even if that implies creating new “superclasses”.

The consequences of these set of criteria will be discussed further in the following sections.

Naming classes of cell types

In parallel to the criteria raised on part 1, I propose a set of naming conventions for different classes of cell types, to facilitate communication. Much of the literature mixes cell types in one species (e.g., when dealing with a cell type as an evolutionary unit) and multispecies (e.g., in the cell ontology). It is arguably useful to distill these different concepts into their own names.. Given the importance of the concept of species in biological classification [29] [30], we derive a “species-centric” view on the naming of classes of cell types. The three classes we propose are:

- Archetypes, for when the *taxonomic scope* of the type is beyond the level of species. For example, “mammal neutrophils.”
- *Stricto sensu* cell types, for when the *taxonomic scope* of the type corresponds to a single species. For example, “human neutrophils.”
- Infratypes, for when the *taxonomic scope* is below the level of species. For example, considering the mouse strain “C57BL/6J” [31], “C57BL/6J neutrophils”.

By adopting a more precise vocabulary, we can flesh out misunderstandings and communicate clearly. At the level of individual scientific experiments, we usually work at the “infratype” level: the samples come only from a subpopulation of the species of interest, and cannot be assumed to be “randomly sampled” from all individuals. This has important practical considerations for, once more, avoiding failing implicitly for the problem of induction.

In addition, in individual experiments, we work with cells of very specific classes. They are not only infratypes, but very specific infratypes, defined by non-random research setups and pragmatic choices. For example, we might call “CD4 T cells” what are actually CD3+, CD4+, CD8+ cells from the axillary lymph node of 2-month-old chow-fed female C57BL6/J mice from the mouse-house of the Institute of Biochemistry of the University of São Paulo collected in several mornings around 10 pm. Albeit really specific, all the mentioned facets (markers, anatomical location, age, biological sex, strain, housing conditions, circadian clock and diet) are known to alter what we know about cell types. Thus, we benefit from using a name for these very specific classes:

- Technotype: A specific, experimentally defined cell type, which harbors on its definitions the precise conditions of the cells sampled.

Even if really specific, a technotype is still a class. Unless a study used only one single-cell, it likely contained some sampling method. Samples are sampled from a specific population, for which hypothesis are actually tested. This is the most “granular” cell type in our pragmatic view for research synthesis. This is the type that can be strictly annotated in single-cell RNA-seq analysis, for example.

Single claims are made and tested for technotypes, and the claims can be logically combined in “upper” ontological levels for making claims with a higher degree of universality. The propagation of knowledge to upper levels cannot be implicit. (see Yarkoni 2020 for an analogous problem in the psychological sciences [32]). As defended by Popper, knowledge should travel “quasi-inductionally” by

fostering hypothesis with higher degrees of generality, which can then be tested for the more universal class [33].

Logical consequences of the definition

One logical consequence of the rules is that concepts of “subtype” become redundant with “cell type.” A “subtype,” then, is a concept that only makes sense when talking about classes with different degrees of universality. Thus, claims to discover new cell “subtypes” or “types” differ only stylistically and can be considered indistinguishable in the perspective of research synthesis.

The cell type as defined here, includes both persistent classes of cells - the traditional cell types - and transient, fugacious classes of cells - often also called states or even programs. Even though such distinctions are important topic for theoretical research, it might not a requirement for representing biomedical experiments. In fact, the fuzzy border of activity (“traditional cell state”) and identity (“traditional cell types”) gene expression programs is acknowledged by the community [34] [35]. Aviv Regev, a co-chair of the Human Cell Atlas mentioned in a recent HCA Latin America Meeting, “in a sense, for any cell, at any moment in time, when you are profiling it, what you are seeing is its state. (...) There is the overall state of the cell, which is made of many different programs, some of which represent this more invariant part of the cell’s identity that we tend to call a type, whereas others are more variable and they can change for a cell of the same type” (<https://youtu.be/1hOwgTH6vZY?list=PLkef4SGmngdbGgJlQh7xDI-lgMZMsl-YJ&t=1089>). The rules proposed here aim at harmonizing these ideas, by explicitly allowing cell type definitions to include descriptors related to activity, identity, or a mix of both.

One example of this entailment is that the class “human cells in metaphase of mitosis” can be considered a cell type, as they can be explicitly defined and restricted to a taxon. Even though “metaphase” itself is a biological process, we can describe all cells executing this process as a single cell type.

However, does a dividing fibroblast stop being a fibroblast, even if temporarily? Again, we do not aim to answer this in a philosophical-ontological sense. Pragmatically, if the explicit definition used for fibroblast (e.g., expression of a marker) still holds during duplication, this cell can be assigned to two classes that are not hierarchically related: “fibroblasts” and “doubling cells”. It is, thus, essential to consider that cells can belong to at least two disjunct classes.

If cells can be assigned to multiple classes that are not hierarchically related, it is not possible to annotate cell types using a single taxonomic tree, in which each concept would be represented by a single node with one (and only one) direct parent node. This is conflicting with attempts to classify cell-types using single hierarchies in the form of a tree [36] [37] [38]. Cell types need to be represented ontologically (in the computational sense), which can be thought of multiple, intertwining trees, which take into account different ways of classifying cells.

Practical consequences of the definition

In the previous section, we discussed the logical entailments of accepting the proposed rules as valid. Here, we will extend the pragmatic considerations on using such a system for real-world applications.

In one recent attempt to define cell types for single cell RNA-Seq, Aevermann et al came up with a set of needs: “The minimum set of necessary and sufficient marker genes selectively expressed by the cell type”, “A parent cell class in the CL”, and “A specimen source description (anatomic structure | species).” [39] They have great merit in defining clear guidelines for marking a cell type. The

requirement of markers is reasonable for the field of single-cell RNA-seq, where marker information is abundant. The Cell Ontology has used markers for defining cell types, an approach specially employed for immune cells [17] [25] [26].

The use of markers, however, leaves us with a conceptual problem: definitions of cell type used by electrophysiologists, or even in the manuals of histology classes, are not based on markers. Rigorously, this would leave aside a whole part of what we consider biomedical knowledge. Moreover, gene markers are not defined for cell types that span multiple species, a problem already discussed on the Cell Ontology report of 2011 [17].

By using our less stringent set of rules, we can better evaluate claims of discovery of new cell types. With vast amounts of data and loose definition of cell types, it becomes uncannily easy to claim a new cell type. Conversely, if one explicitly claims to discover a new “*stricto sensu*” cell type, one has to provide enough evidence that cells from this class are identifiable across all individuals of a species. A claim of an “archetype” would require evidence for existence in more than one species. Consequently, experiments that only use a specific strain of mice have a stronger claim if the expectation is limited to the infratype.

An example of the discovery of a new “archetype” is the pair of articles published in Nature in 2018 [40] [41] about the newly found “ionocyte”, a class of cells in the trachea enriched for expression of genes homologous to the *CFTR* gene. Both studies displayed evidence for such a class in both mouse and human samples, corroborating the existence of an archetype. This discovery of an archetype has been denominated by both articles as a discovery of a new cell type.

Another example of cell type discovery is a pioneer article by Villani et al [42]. It describes subclasses of monocytes and dendritic cells in humans, and pragmatically uses markers for their definition. The patients were recruited from “the Boston-based PhenoGenetic project (...) and the Newcastle community.” It is arguable that they did not have a random sample of humanity, and the observed results might not hold for different populations. This discovery of infratypes has also been described as a discovery of a new “cell type”.

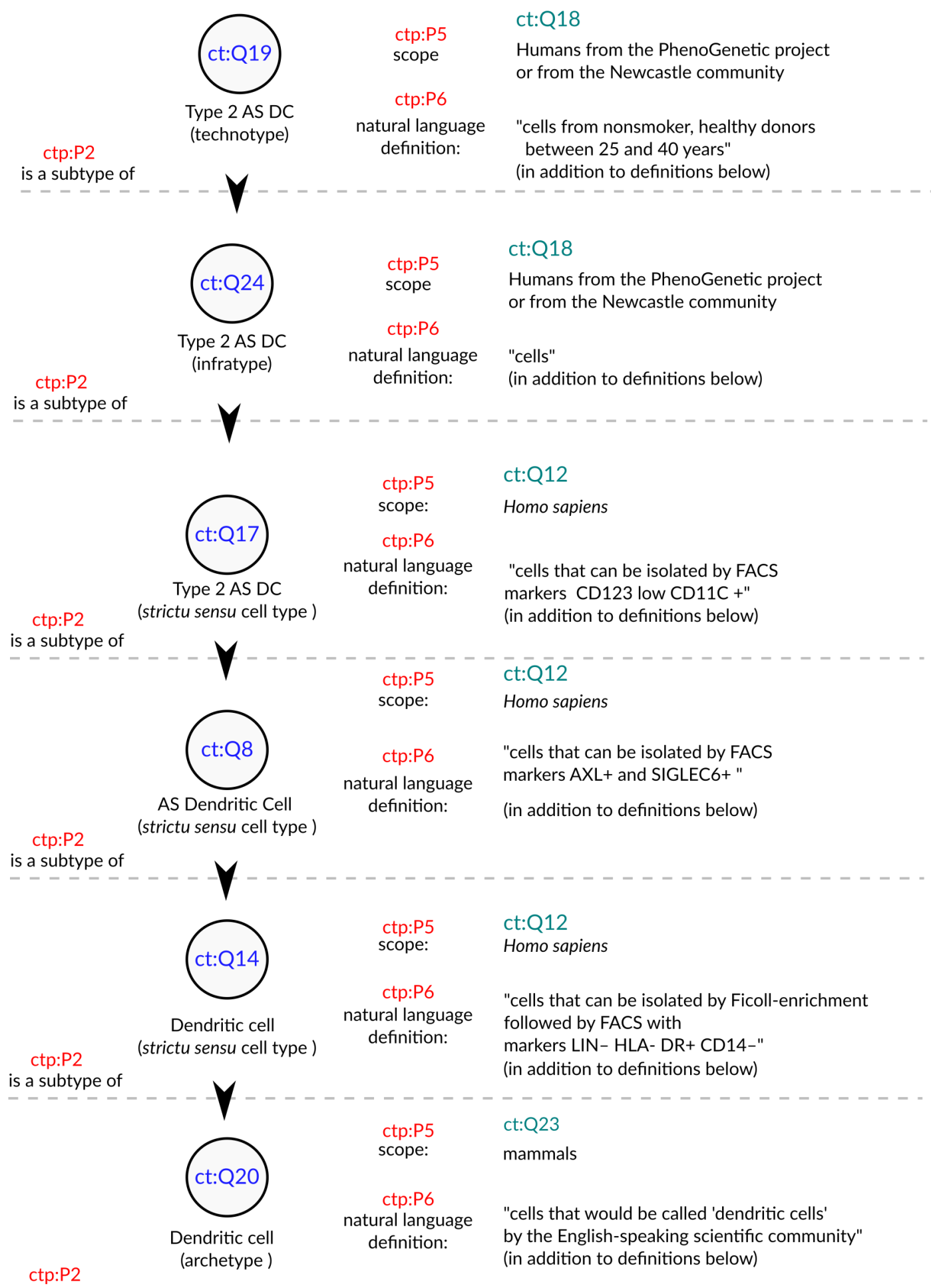
An example from the article is the discovery of the “AS Dendritic cell” (and two subpopulations of it), characterized by expression of the antigens for the proteins AXL and SIGLEC6. This and other cell types are presented in the article as part of a “Human dendritic cell atlas”, generalizing the theory for the whole humanity. However, it is not clear if the population sampled included individuals from different human background. Thus, it is technically possible that the existence of the “cell type” exactly as described might be restricted to some human groups. The jump from technotype (which takes into consideration also descriptors like “healthy” and “age between 25 and 40 years”) to infratype (“all humans in this population scope”) to cell type *strictu sensu* (all humans) is depicted in the figure 1 and exemplifies the logical flow.

“Dendritic cells” is one of the cell types most thoroughly modelled by Cell Ontology. [43] [44]. The current natural language definition of dendritic cell (CL 0000451) states that a dendritic cell is “A cell of hematopoietic origin, typically resident in particular tissues, specialized in the uptake, processing, and transport of antigens to lymph nodes for the purpose of stimulating an immune response via T cell activation. These cells are lineage negative (CD3-negative, CD19-negative, CD34-negative, and CD56-negative).” The structured definitions are derived from the leukocyte (CL 0000738) definition, which defines such cells as “achromatic cell of the myeloid or lymphoid lineages capable of ameboid movement.” These definitions are not reconcilable to the “dendritic cells” studied by Villani et al’s. We have no way of knowing if the cells in their work are “typically resident in particular tissues”, “achromatic” or “capable of ameboid movement”. That might sound pedantic, and might unfortunately be, but the logical requirements of computational systems leads to both [biocurators](#)

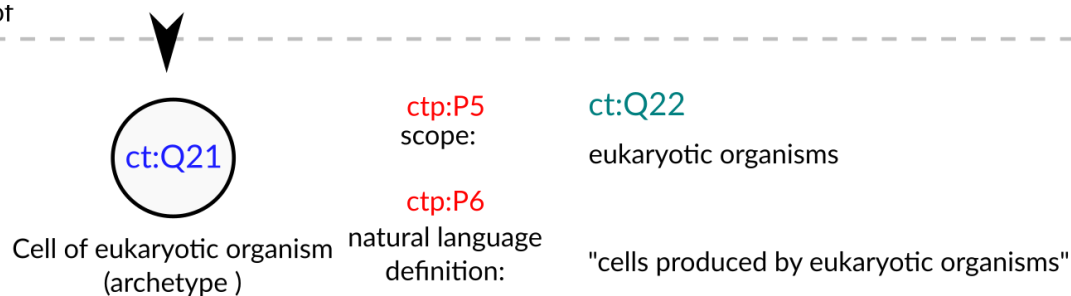
and [computers](#) being seen as pedantic. This high level of precision is necessary to accurately depict not only the complexities of cell types, but the complexities of research settings.

@prefix ct : <<https://celltypes.wiki.opencura.com/wiki/Item:>> .

@prefix ctp : <<https://celltypes.wiki.opencura.com/wiki/Property:>> .



is a subtype of



* Natural language names only unambiguous for cell types conceptualized in Villani et al 2017

Figure 1: Conceptualization of a set of the cell types in Villani et al, 2017 [42]. The depicted cell types were manually curated from the article, where they are either implicitly or explicitly mentioned. The set of cell types is not comprehensive, and represent only a small fraction of the concepts handled by the authors. Identifiers for cell types are written in pseudocode based on the Turtle serialization for RDF knowledge graphs (<https://www.w3.org/TR/turtle/>) and represent valid URIs (described in the database https://celltypes.wiki.opencura.com/wiki/Main_Page). URI: Universal Resource Identifier; RDF: Resource Description Framework.

Even if we are not yet able to formally represent all the aspects that go into a cell type definition, we can use an explicit “natural language definition” property to define cell types. As David Osumi-Sutherland puts in his 2017 article about cell type classification, there is a “*mismatch between quantified logic, which records assertions about all members of a class, and the messy, noisy reality of biology and the data we collect about it.*” [27]. We do not need to have all of biology classified before we deal with cell types. Taking as example in figure 1, all cell types treated as “dendritic cells” in the literature are valid subclasses of the dendritic cell archetype (ct:Q20). Such a subclassing system might lack the power to computationally check the validity of definitions. However, by the principle of minimal commitment [???], it could already be a suitable scaffold for representing experimental data (e.g from single-cell transcriptomics) and allow logically robust data integration.

Sabina Leonelli stated that the challenges brought up by big data in biology require an advance of our philosophical theories [45]. We agree, and argue that the inverse is also true: to advance the theoretical foundations of modern biology, we need to harness the power of computational tools. Computational ontologies provide a solution for dealing with complex concepts. Classes in ontologies can have alpha-numeric identifiers. We can, thus assign each technotype a Unique Resource Identifier, a URI, similar to the Cell Ontology (CL) [16] [17] [18] or Wikidata [46] [47]. The power of using knowledge bases for integrating knowledge about cell types is becoming clear [12], and its success relies heavily on precise usage of unique identifiers.

The quest for names/labels systems for types is related to the quest for defining cell types, and exciting proposals are already arising. [48] [49] Nevertheless, the definition of rules for *naming* cell types is outside the scope of this article, and abstracted away via semantically void identifiers. A semantically void identifier, in contrast to rule-based numeric identifiers[50] or natural language names (such as Latin scientific names for species) is resilient to changes in our knowledge. It also floats away from the problems of essence-indicating and role-indicating names discussed by Rowe and Stone in 1977[51]. Complementary to being non-descriptive, identifiers can be assigned labels, which can be freely changed, while keeping a persistent Universal Resource Identifier. We devoted our effort to refining the logical aspects of cell-type definitions, which might be combined with any commonly agreed naming/labeling system.

The level of “technotype” allows precise labeling of cell types in real world experiments. The non-existence of truly exact matches in CL (even when combined with other ontologies) renders it theoretically impossible to annotate articles and datasets with perfection. The “technotype” gives

power to every researcher to craft their “cell type” of interest and connect it to a common network of knowledge.

Specifically, for single-cell transcriptomics, the technotype refines our model for labeling cells (and, consequently, cell clusters). A branch of computational single-cell development has dedicated itself to find tools for labeling single-cell experiments. While some approaches ignore ontologies [36] [52], others aim at finding the best class among the Cell Ontology [53] [54] or MeSH IDs[55] [56]. Manual matches to the Cell Ontology have been fed to algorithms such as BLAST2CO [56] and OnClass [57] to predict best “matches” for a single-cell RNA-seq cells or clusters. However, unless the cells were sampled in the same way across articles, and drawn at random from the same population of individuals, they represent strictly different classes, even if very similar. Thus, we must change the task from finding a “match” to the cells in a given current experiment to finding a “point of insertion” in an ontological network. By acknowledging these real differences, we can have precise metadata, enabling precise statements and facilitating valid reuse of publically available data.

An Occam`s razor argument for the use of the technotype is that it makes data integration a simple task. Let a *stricto sensu* human type X be *completely* defined by “any cell that expresses the *CD4* gene, but not the *CD8A* gene”. A definition of this kind allows detection via both mRNA or proteins, as both are evidence that a cell is *expressing* a gene. Then, only the information about these two genes is used, and the analyst has only to decide what is the threshold for considering a gene as expressed. All cells that matches such pattern would be assigned to a technotype Y, where Y is a subclass of the *stricto sensu* human type X. Each cell could receive more than one label (depending on the masks applied to the dataset).

Some cells of interest could be missed, especially taking into account dropouts in single-cell. However, with a carefully crafted set of necessary markers, such features can be explicitly accounted for. A cell type definition can employ any logical relation, including “OR”. A cell type W can be defined as any cell that expresses the *MS4A1* gene OR the *CD79A* gene”. Once such a marker-based definition is decided by the researcher given their research questions, it can be easily tested for any cell, regardless of the size of the dataset. In computational terms, regarding an increasing number of features in the dataset, the mask algorithm scales in big O(1), and regarding the number of cells (provided that you want to label all cells) in big O(n). If there is no information about the expression of “*MS4A1* gene OR the *CD79A* gene”, no cell in the dataset can be assigned to *exactly* this cell type, and another classes need to be employed. Our flexible, yet rigorous, framework for defining cell types can help us to deal with the challenges of varying resolution levels of interest and the scaling large datasets.
[doi:10.1186/s13059-020-1926-6]

Such a rule based system enables interpretable data-driven cell-type classifications, in contrast to the previously proposed cell type definitions by reference expression matrices with tens of thousands of genes. Furthermore, it makes the task of *identification* of cell types almost trivial: you only know what you measure, and that can be checked against an explicit and complete definition (containing the features that are necessary and sufficient for an identification). Any logical entailments (e.g : a cell that expresses CD3 is achromatic) must be acknowledge explicitly too, if we want to use them for classification and identification. The need of an identification routine for cell-type taxonomies is acknowledge for more than 45 years [58], and still is a core challenge of human cell-type atlases [doi:10.1186/s13059-020-1926-6]. The quest for data-driven cell classification is at least as old [58]. The framework here proposed provides ideas to improve our solutions to both tasks.

Final remarks

In this article, we proposed a set of 3 rules (rigorous description, taxon scope restriction, and theoretical usefulness) and 1 recommendation (hierarchical link to other cell types) to define cell

types. We also proposed 4 namings to clarify discussions on the topic: archetypes (a class with a scope above species level), *stricto sensu* cell types (a class with scope equal to one species), infratypes (a class with scope below the species level) and technotypes (the exact cell type defined for an experimental setup). The concept of the “technotype” can be harnessed as a fundamental taxonomic unit for classifying cells, in an analogous way of how the “species” is the conventional unit for classifying organisms into higher-order taxa.

We dissected some logical entailments of such definition, which, admittedly, might conflict with current views on defining cell types. We do not aim at solving such conflicts, or negating the other perspectives, but only propose a different way of organizing our knowledge about cell types.

This article clarifies some of the meanings and provide directions to the future development of the theoretical basis of cell type definition. The discussion on cell types’ definition is still on its infancy, and we need human power to tackle this huge theoretical challenges. Biologists, philosophers, and computer scientists ought to distill the details of defining cell types, powering the Human Cell Atlas, and the life sciences research enterprise of this century.

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Supplementary notes which did not end in the text

A set of notes that may be incorporated into the final text, or become appendices, or end up as blog posts somewhere.

What to do when two researchers disagree on a definition?

Cell type names are notoriously ambiguous and one definition might collide with an other, specially regarding the natural language name used to described. There are many different, equally valid definitions of a “dendritic cell.” we do not aim to solve this problem from a societal standpoint. However, from a computational-ontology standpoint, there is one simple solution: split the concept.

This approach is similar to King Solomon’s solution in a famous bible story, called the [Judgement of Solomon](#). In a dispute between two women that claimed to be the mothers of a child, the solution of the king was simple: split the baby. However, babies are notoriously indivisible, and the true mother did not really like the idea.

It may be that some scientists are attached to their names, as mothers are to their babies. However, unlike babies, namings can be divided. Each of the scientists gets to name their specific

conceptualization however they choose. Many names might “collide” in that way, and that is okay. Under the hood, however, the names refer to different identifiers. Computationally there would be no ambiguity. Then, it is just a matter of the researcher to respect the choice of their peers of calling something by the *wrong* name, as long as the identifier is correct.

Splitting concepts upon conflicts in the end is more the multiplication of bread and fish in the [Feeding the multitude](#) episode, and everyone gets to eat.

But ontologies are different from ordinary babies and magical fish. The splitting of concepts would not only create new concepts, but leave a trace. They would be immediate subclasses of their conjunction. An equally valid superclass that can be defined by “a cell containing characteristics of any of their subclasses”.

In a parallel with text-book mitosis, the concept gets divided in two new, equally real concepts. And as we can trace cells in an animal to a single zygote, we can keep track of concepts while they keep dividing, whenever a new conflict pops up.

The big assumption of continuity in time

One assumption that underlies the validity of the models proposed here is that taxons preserve their characteristics throughout time.

In Popper’s Logic of Scientific Research, he states that he has a metaphysical faith on the continuity of laws of nature through time.

We have no way of testing this metaphysical faith, and it is absolutely necessary for the scientific endeavour as we understand.

While in physics this assumption seems to be reasonable, evolution makes biology quite more complicated. Statements that we have about the human species, for example, might be valid today, but were not valid 2000 years ago, and vice-versa.

When we talk about sub-species taxons, which might be a local population of a town, for example, this unit is not immutable. The population of Newcastle, as per the example, might change in time, with immigration and emigration, mutation, natural selection, neutral evolution and the many forms of modifications of a gene pool.

It is, thus, and heuristic, to call “population of Newcastle” a class. We could specify a period in time for which we expect the information to be valid. For example, we may say we are sampling from “the Newcastle population in the years 2019-2020.” This would be a valid statement, but it would not be falsifiable, as by 1st of January 2021, no independent tests of the theory can be done.

It is technically possible to have a technotype so precise as to have a scope with a time constraint. In fact, that might be the right way of representing information, if we want to compare experiments done in evolving populations.

While evolutionary definitions take this dimension into account, they are fit to theoretical research, but still lack the rigour for explaining real world experiments.

All research that uses human samples are subject to strong influence of time.

Thus, the explicit assumption here is that taxons are consistent in time. And, for what we know, it is blatantly false.

This is a great flaw of the model, and, maybe, of a great part of biomedical research. The logical consequences are so dire, that it merits a separate, dedicated work.

Clusters are not cells

In the era of large-scale omics, we are starting to see declarations of cell types that are not based on pre-selected criteria, but derived from unsupervised clustering followed by labelling.

This is a powerful exploratory approach, which, as mentioned in the main text, has led to discoveries of ionocytes and new classes of dendritic cells, for example.

Many algorithms and “expert-based” annotation protocols focus on labeling *clusters* instead of labeling *cells*.

Cells in a cluster are arbitrarily similar (as determined by the clustering algorithm) and so they will, by definition, differ from other cells in the sample.

For single-cell RNA-seq, one usually checks which genes are differentially expressed when comparing the cells in a cluster with cells in other clusters. These genes are called “markers” and used for labeling a cell cluster.

What does it mean to label a cell cluster, though? Does it mean that *all* cells there conform to the cell type? Does it mean that *most* cells there conform to the cell type? Does it mean that cells from other clusters in the dataset *definitely do not* conform to the cell type?

So far, we haven’t seem a clear, explicit, coherent definition for a cluster label. Not even once.

Marker-based definitions are assumed for the group as a whole, but in current pipelines, nothing blocks one cell in a cluster to lack the expression of a “name-giver” marker.

The classification scheme proposed here works to classify *cells*, but is not sufficient for labeling unsupervisedly-defined *cell clusters*.

What is possible, though, is to use clustering for data exploration. From then on, strict patterns can be decided (ex: a cell that expresses A and B, but not C) and then apply this pattern to the whole dataset. For clusters with consistent markers, this approach should be roughly equivalent to the previously described.

Using such “regular expressions” might lead to a cell being assigned to multiple clusters. Even if we assume that the sample is free of doublets, that cannot be a problem. Cells may have multiple functions. As argued in the main text, each cell can be labeled by multiple standards.

We may avoid multiple labeling if we really need in practice, though, and make preferential claims (if a cell matches definitions X and Y, it is assigned only to X, for example).

By having explicit “regular expression” patterns for cell definitions in single-cell datasets, the “cell-type assessment” problem becomes trivial: a cell in a new dataset is of the *exact* same type if (and only if) it matches the *exact* definition.

When that is not the case, current algorithms for reconciling single cell datasets can still be successfully employed. But instead of propagating a label, it would propagate a parent class, looking for cells of a similar, sister class.

What this work is not

This is not an attempt to substitute the Cell Ontology (CL) or contradict it in any way. CL is an amazing resource, built by a community of wonderful researchers. Its relation with CL is coexistential, and topics discussed here might be or might not be of interest of CL, and that is OK.

This is not an attempt to create an ontology itself, or a system that allows reasoning. It is a set of suggestions that can be taken into consideration for building a coherent ontology. The [Cell Type Wikibase](#) is an experimental ontology, and far from ready for professional use.

This is not an attempt to have a one-size-fits-all definition of cell type. It is built as a theoretical solution for one cell-type related task. Similar to species definitions, we need an ecosystem of cell-type and cell state definitions that better suit different areas.

This is not an attempt to claim anything about the “true” nature of cell types, in the biological sense. It is a proposal of practical guidelines to represent research data.

This is not an attempt to solve *all* problems for cell type data annotation. It is the introduction of alternatives that need to be further developed and discussed.

Immune Epithope DB

The Immune Epitope Database and Analysis Resource (IEDB) announced it in 2006 [doi:10.1371/journal.pcbi.0020125]:

“the goal of the IEDB is to present as much information as possible without subjective interpretation, we can never presume any information, but rather we must try to capture the data exactly as presented in the reference, while maintaining the conclusions of the reference in a uniform manner. For example, if all experiments are performed with a whole cell population, but the authors attribute the response to a particular cell type without any evidence, we must capture the effector cells as the entire population.”

That is the kind of challenge that the “technotype” solves in theory, as it gets the objective population sampled in any article.

Phenetic Species Concept

The Phenetic Species Concept states that species are the smallest groups that are consistently and persistently distinct and distinguishable by ordinary means. Maybe that is crosslinkable.

The link between the phenetic species concept and the classification of cell types has been noted before. [59] The ideas of explicit definitions and hierarchical relations resound with the goals of this article.

In this work [59], they mention 5 facets of phenetic systematics: - Group (that is, ‘type’) membership should be based on multiple criteria rather than on a single so-called ‘essential’ feature that the

investigator favours. - The criteria for group membership should be rule-based, explicit and quantitative. - Groupings should be hierarchical rather than flat to acknowledge the validity of both coarse and fine divisions. - Groupings generated by this approach should be viewed as hypotheses to be tested rather than inflexible rules. - Classification should focus on discontinuities between groups and ignore parameters that vary continuously.

Calculation of theoretical maxima and minima of human cell types

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