

Manuscript Title

This manuscript ([permalink](#)) was automatically generated from [lubianat/phd_thesis@1a3070c](#) on April 17, 2021.

Authors

- **John Doe**

 [XXXX-XXXX-XXXX-XXXX](#) ·  [johndoe](#) ·  [johndoe](#)

Department of Something, University of Whatever · Funded by Grant XXXXXXXX

- **Jane Roe**

 [XXXX-XXXX-XXXX-XXXX](#) ·  [janeroe](#)

Department of Something, University of Whatever; Department of Whatever, University of Something

Master index

Numbers are used as tags for literature and should not be changed!

At best, names can be clarified.

Ex: 1.1.2 refers to “Interoperable data: dataset integration”

Order may be changed at a later step.

- 1. Introduction
- 1.1. The quest for interoperable knowledge
 - 1.1.1. Literature Based Discovery, hidden knowledge and text-mining
 - 1.1.2. Interoperable data: dataset integration
 - 1.1.3. Interoperable publication processes: nanopublications
- 1.2. Formal representation of knowledge
 - 1.2.1. Descriptive logic and its historical context
 - 1.2.2. Computational ontologies and their methods
 - 1.2.3. Web of Data and Linked Open Data
 - 1.2.4. Wikidata and Knowledge Graphs
 - 1.2.5. The role of definitions in formal knowledge
- 1.3. Knowledge Representation in biology
 - 1.3.1. OBO Foundry and biomedical ontologies
 - 1.3.1.1 Gene Ontology
 - 1.3.1.2. UBERON
 - 1.3.1.3. MONDO and DO
 - 1.3.1.4. Cell Ontology (and CELDA)
 - 1.3.1.5. UMLS, NCIT and non-OBO resources
 -

- 1.3.2. Biological knowledgebases
- 1.3.2.1. Cell-type-oriented knowledgebases
- 1.3.2.2. Other databases relevant for this work
- 1.3.2.3. Bio2RDF and semantic databases
-
- 1.3.3. Wikidata as a platform for representation of biological knowledge
-
- 1.3.4 Semantic Systems Biology
- 1.4. The challenges of the Human Cell Atlas
- 1.4.1. The Human Cell Atlas project and its scope
- 1.4.1.1. Participants
- 1.4.1.2. Overview of main analytical techniques
-
- 1.4.2. A focus on single-cell RNA sequencing
- 1.4.2.1. Wet-lab methods and their differences
- 1.4.2.1.1 Bias introduced by different scRNA-seq methods
- 1.4.2.2. Computational analysis of scRNA-seq data
- 1.4.2.2.1. Clustering algorithms
- 1.4.2.3. Cell label identification
- 1.4.2.3.1. Labelling clusters
- 1.4.2.3.2. Labelling events
-
- 1.4.3. Data availability
- 1.4.3.1. As coordinated by the Human Cell Atlas
- 1.4.3.2. By the community as a whole
-

- 1.4.4. Types of knowledge about cell types
-
- 1.4.5. Goals of this project
- 2. Definitions
- 2.1. The concept of “gene”
- 2.1.1. Gene as phenotype x gene as DNA
- 2.1.2. Species-specific genes and multispecies genes
- 2.1.3. Representations of genes in knowledge bases
- 2.1.4. A simple theory of the molecular gene
- 2.1.4.1. Allele x gene
- 2.1.4.2. Gene as individual and gene as a class
- 2.2. The concept of “taxon”
- 2.2.1. Lines of thought about the taxon concept
- 2.2.1.1. Cladistics and the PhyloCode
- 2.2.1.2. Phenetics and Numeric Taxonomy
- 2.2.2. Bacteria, cell lines and the plurality of the concept of taxon
- 2.3. The concept of “cell”
- 2.3.1. Historical perspective
- 2.3.2. Boundaries of the concept in the context of this thesis
-
- 2.4 The concept of “cell type”
- 2.4.1. Historical perspective and the morphological cell type
- 2.4.2. Modern perspectives of classification of cells
- 2.4.2.1. Classification
- 2.4.2.1.1 Evolutionary cell types
- 2.4.2.2. Identification

- 2.4.2.2.1. Transgenic animals and marker-based identification
- 2.4.2.2.2. A posteriori identification in high-throughput methodologies
- 2.4.2.3. Nomenclature
- 2.4.3. States, identities, fates, attractors and phenotypical continuity
- 2.4.4. A pragmatic definition of cell type
 - 2.4.4.1. 3+1 rules for defining one type
 - 2.4.4.1.1 Cell types must have explicit definitions
 - 2.4.4.1.2 Cell types must have a taxonomic scope
 - 2.4.4.1.3 Cell types must be useful
 - 2.4.4.1.4 Cell types should be inserted in an ontology
 - 2.4.4.2. Names for different classes of types
 - 2.4.4.2.1 The cell archetype
 - 2.4.4.2.2 The sensu stricto cell type
 - 2.4.4.2.3 The infratype
 - 2.4.4.2.4 The technotype
 - 2.4.4.3. Logical implications of the definition
 - 2.4.4.4. Practical implications of the definition
 - 2.4.4.5. Less-strict, literature based definitions for immediate use
 - 2.4.5.1. The use of the concept in the literature
 - 2.4.5.2. The use of the concept in metadata and knowledgebases
 - 2.4.5.3. The use of the concept in ontologies
 - 2.4.5.4. Wikidata and consensus-determined rigorously undefined concepts
- 2.4.6. Claims of novel cell types
- 2.5. The concept of “protein”
 - 2.5.1. Proteins, proteins families and protein molecules
 - 2.5.2. Protein complexes and their details

- 2.5.3. Protein forms
- 2.6. The concept of “transcript”
- 2.6.1. Transcript expression x gene expression x protein expression
- 2.7. The concept of “cell marker”
- 3. Practical Projects
- 3.1. Cell-type markers in Wikidata
- 3.1.1. PanglaoDB
- 3.1.2. Other bases of markers
- 3.1.3. WikidataMarkers: a website and an R package for cell type gene sets
- 3.1.4. Cell-Disease networks via Wikidata
- 3.2. Community annotation of texts via Wikidata
- 3.2.1. Pilot: Annotation of the Human Cell Atlas corpus
- 3.2.2. Community curation and gamified science
- 3.2.2.1. ANN
- 3.2.3. Text mining and Wikidata community curation
- 3.3. Cellosaurus cell-lines to Wikidata
- 3.4. Single-cell RNA-seq data reconciliation to Wikidata
- 3.4.1. Integration of single-cell RNA-seq bibliometric data to Scholia
- 3.4.2. scRNA-seq metadata reconciliation
- 3.4.2.1. COVID-19 cell types collection
- 3.4.2.2. Other single-cell RNA-seq datasets
- 3.5. Practical applications of a pragmatic cell type definition in 2.4.4
- 3.5.1. Basic dictionary for cell type identification based on regular expression of cell type markers
- 3.5.2. R package for suggestion of cell-type rules based on Seurat clusters
- 3.5.3. R package for rule-based identification of cell types
- 3.5.3.1. Data model and development

- 3.5.3.2. Large scale application to many datasets
- 3.6. Wikidata Bib and scientific practice as a first-class citizen in the knowledge world
- 3.6.1. The Wikidata Bib platform and the formalization of a reading discipline
- 3.6.2. Linked Open Data for personalized analysis of bibliography
- 3.6.3 Sowing the seeds of knowledge: Meta contributions to Wikidata during the PhD
- 3.7 Scholarly and metascientific information on Scholia/Wikidata
- 3.8 The long tail of biocuration
- 3.9 Semantic Systems and Synthetic Biology
- 3.10 Minimal Information About New Cell Classes
- 0 Master's projects
- 0.1 fcoex & FCBF
- 0.2 Alexa
- 0.3 PubScore

Abstract

The Human Cell Atlas is an international effort aiming at characterizing every cell type of the human body. Employing techniques such as single-cell RNA sequencing, mass cytometry, and multiplexed in situ hybridization, it will produce data from virtually all human tissues. This wealth of data can have a significant impact on biomedical research, but only if its content is genuinely available. Wikidata is a knowledge graph database emerging as a FAIR (Findable, Accessible, Interoperable and Reusable) repository for biological knowledge. The formatting and deployment of information from the Human Cell Atlas to Wikidata can increase information availability and impact, by inserting the findings in a network containing multiple associations of concepts of all areas of knowledge (within and outside science). Conceptually defining cell types in a general and applicable concept, formalized into a database-compatible format, is a massive theoretical challenge. This PhD project aims at studying our current understanding of cell types for development a comprehensive ontological model in Wikidata for cell types. We will review the single-cell literature, refining and formalizing concepts for cell type delimitation. Furthermore, we will use Natural Language Processing and Machine Learning tools to automate knowledge extraction from scientific articles in the scope of the Human Cell Atlas. In an advanced step, we will apply concepts of network theory to develop tools for user-friendly querying of the database, making the knowledge ready for the academic community.

Introduction

The Human Cell Atlas (HCA) Project

The advent of single-cell technologies has ignited the desire of a deep knowledge on cells, the building blocks of life [1]. The Human Cell Atlas (HCA) project, has been a major player in the cell knowledge ecosystem, running since 2017 towards the task to characterize every cell type in the human body [2]. The HCA consortium recruited people from all over the world to tackle different parts of the project. In Brazil, Prof. Helder Nakaya (supervisor of this PhD project) is leading the national effort to contribute to HCA, with a focus on the roles of different cell types in the pathological processes of infectious and inflammatory diseases.

Building a full atlas of human cells comes with multiple challenges. The project includes detection, in single cells, of RNA content (scRNA-Seq), chromatin accessibility (scATAC-Seq), and protein markers (primarily by CYTOF), as well as spatial information on cells with multiplexed *in situ* hybridization (such as MERFISH) and imaging mass cytometry [2,3]. Every lab will contribute with its expertise, providing samples that are representative of human diversity.

HCA is set to revolutionize the biomedical sciences, by creating tools and standards for basic research, as well as allowing better characterization of disease, and thus, ultimately, improving diagnostics and therapy. Its products (data, information, knowledge and wisdom) need to be FAIR: findable, accessible, interoperable and reusable. Data stewardship and data management are growing as core demands of the scientific community, ranging from data management plans [4] to specialized personnel [4].

The Human Cell Atlas has a dedicated team for organizing data: the Data Coordination Platform (DCP) [5] [3]. The DCP is responsible for tracing the plan for computational interoperability, from the data generators to the consumers.[3]. The Human Cell Atlas has its portal for data (<https://data.humancellatlas.org/>) which composes the data repository landscape with other resources, like the Broad Institute Single Cell Portal (https://singlecell.broadinstitute.org/single_cell) and the Chan-Zuckerberg Biohub Tabula Sapiens (<https://tabula-sapiens-portal.ds.czbiohub.org/>). In addition to its core team, the HCA is poised to grow by community interaction, and states in its opening paper that “As with the Human Genome Project, a robust plan will best emerge from wide-ranging scientific discussions and careful planning”. [2] Thus, this project inserts itself among the wide-ranging scientific discussions to improve data - and knowledge - interoperability.

The highlight of “knowledge” in the last paragraph is meant to stress that data *per se* is not enough. There is a long way from raw datasets to commonly agreed scientific knowledge. And, ultimately, this long way is what allows humanity to take advantage of scientific endeavors. Currently, the gap between data and knowledge is mostly targeted via the writing and sharing of scientific manuscripts, the *de facto* currency of exchange of claims about the natural world. The Human Cell Atlas Publication Committee reviews and selects publications that are directly part of the HCA. A set of publications is, thus, one of the major outputs of the whole endeavor.

The challenge that arises, thus, is one of managing a wealth of information and cast it into useful science. Experimental articles that analyze thousands of cells pose an overload of information alone. Ideally, we would like to understand, remember and make use of every statement produced by the HCA. As this goal is humanely impossible, we need to develop tools to make the knowledge interoperable with the aid of computers. At that point, the challenges of the HCA enter in resonance with the challenges of text-mining, biocuration and literature based discovery, which will be discussed in the chapter of this introduction. ## Literature Based Discovery, hidden knowledge and text-mining

- Tsunami of knowledge - o parse, connect and benefit society
- Literature based discovery is a way to connect knowledge
 - Biocuration and organization
 - Actual processing of the curated information

Knowledge graphs as tools for interoperability

- The OBO Foundry and biomedical ontologies
- Knowledge graphs and a different approach to biomedical semantics
- Wikidata as a knowledge graph for the life sciences

Objectives

- Set up the semantic infrastructure on Wikidata for handling knowledge about cell types
 - Refine the theories of types/states/classes of cells within the constraints of ontologies and knowledge bases
 - Investigate the types of statements done about cell types
 - On Wikidata
 - On OBO Foundry ontologies
 - Freely on the biomedical literature
 - Craft wikidata relations (“properties”) for making cell-type-related assertions (like “has marker” or “is the progenitor of”)
- Devise ways to connect the Human Cell Atlas products to Wikidata and the Linked Open Data cloud
 - Write bots and scripts to reconcile data sources to Wikidata
 - Create tools for biocuration of Human Cell Atlas products combining text mining and expert curation
 - Project software for reuse of HCA-related knowledge integrated into common bioinformatics workflows.
- Provide proofs-of-concepts of how Wikidata integration can benefit the advancement of HCA

Methodology

Organized reading

Given the breadth of the task envisioned for this project, a standard methodology of reading was followed.

- Describe Wikidata bib
- Integrate with ECO's views

Wikidata updates

- Property proposals
- Wikidata bots
- PanglaoDB integration
- Semi-manual integration: Google Sheets and Quickstatements

Data retrieval

-
- SPARQL queries

Data analysis

- Packages used in R and Python
- For interacting with Wikidata

Annotation of Human Cell Atlas articles

Status of cell type info on Wikidata

Cell-disease network analysis

Preliminary Results

The concept of cell type

- Describe background
- Cell types, cell states and cell classes
- Levels of cell type information: archetype, senso stritu cell type, infratype and technotype.
- Infratypes and technotypes as theoretical innovations
- Current usage mixes archetypes and species-specific cell types
- Annotation of HCA articles for grasping the use of different concepts in the context of HCA

Next steps

- Improve formalization of cell types in connection with the biomedical semantics community

HCA

- “Sky dive” approach: hand annotation of all abstracts and the core Human Cell Atlas paper
- Benefits of using a single ontology that anyone can edit (new terms and speed of science)
- Figure: The different concepts in use by the HCA paper
- Figure: The different concepts in use by the different HCA papers
- Discussion
- Information by HCA and related efforts is already targeted by biocurators. PanglaoDB is one of these resources etc etc

Next steps

- Mature the annotation system into a curation tool (based on ANN, perhaps reuse figure)
- Explore the use of SciSpacy and natural language processing for making it easier

PanglaoDB integration to Wikidata

- The architecture of marker information on Wikidata
- Integration of information to the larger scope -> live updates by everyone
- Overview of the stats

Cell-disease networks

- Systems-biology explorations: what can we discover based on the literature distilled on wikidata?
- Cell-disease networks based on shared genes
- Hub diseases and cell types
- ShinyApp to explore the data in real time

References

1. An era of single-cell genomics consortia

Yoshinari Ando, Andrew Tae-Jun Kwon, Jay W. Shin

Experimental and Molecular Medicine (2020-09-15) <https://www.wikidata.org/wiki/Q99418649>

DOI: [10.1038/s12276-020-0409-x](https://doi.org/10.1038/s12276-020-0409-x)

2. The Human Cell Atlas.

Aviv Regev, Sarah Teichmann, Eric Lander, Amir Giladi, Christophe Benoist, Ewan Birney, Bernd Bodenmiller, Peter Campbell, Piero Carninci, Menna R. Clatworthy, ... Human Cell Atlas Meeting Participants

eLife (2017-12-05) <https://www.wikidata.org/wiki/Q46368626>

DOI: [10.7554/elife.27041](https://doi.org/10.7554/elife.27041)

3. The Human Cell Atlas White Paper

Aviv Regev, Sarah Teichmann, Orit Rozenblatt-Rosen, Michael J. T. Stubbington, Kristin Ardlie, Amir Giladi, Paola Arlotta, Gary Bader, Christophe Benoist, Moshe Biton, ... Human Cell Atlas Organizing Committee

(2018-10-11) <https://www.wikidata.org/wiki/Q104450645>

4. Everyone needs a data-management plan

Nature

(2018-03-15) <https://www.wikidata.org/wiki/Q56524391>

DOI: [10.1038/d41586-018-03065-z](https://doi.org/10.1038/d41586-018-03065-z)

5. About the Data Coordination Platform

HCA Data Portal

<https://data.humancellatlas.org/about/>