The Ontology for Avida digital evolution platform (OntoAvida)

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Abstract

The Ontology for Avida (OntoAvida) aims to develop an integrated vocabulary for the description of Avida, the most widely used computational approach for performing experimental evolution using digital organisms—self-replicating computer programs that evolve within a user-defined computational environment. The lack of a clearly defined vocabulary makes some biologists feel reluctant to embrace the field of digital evolution. This unique ontology has the potential to change this picture overnight. In addition, OntoAvida allows researchers to make inference based on certain rules and constraints, facilitate the reproducibility of *in silico* evolution experiments and trace the provenance of the data stored in AvidaDB—an RDF database containing the genomes, transcriptomes, and phenotypes of more than a million digital organisms.

Keywords.

artificial life | digital organisms | experimental evolution | semantic database | web ontology language

1 Introduction.

Since the pioneering work by Thomas S. Ray (1991) 30 years ago, digital evolution research has established itself as a valuable approach in biology, bridging experimental research with computational modelling. The contribution of digital evolution to the development of ecology and evolutionary biology comprises diverse topics such as robustness and evolvability (Edlund and Adami, 2004; Lenski *et al.*, 2006; Elena *et al.*, 2007; Elena and Sanjuán, 2008; Fortuna *et al.*, 2017), complexity (Ray, 1997; Lenski *et al.*, 1999; Adami *et al.*, 2000; Gerlee and Lundh, 2008; Ofria *et al.*, 2008), phenotypic plasticity (Clune *et al.*, 2007; Lalejini *et al.*, 2021), the role historical contingency in evolution (Hagstrom *et al.*, 2004; Wagenaar and Adami, 2004; Lenski, 2009; Clune *et al.*, 2012), ecological interactions among species (Cooper and Ofria, 2003; Johnson and Wilke, 2004; Zaman, Devangam, and Ofria, 2011; Fortuna *et al.*, 2013; Zaman *et al.*, 2014; Dolson and Ofria, 2021), gene regulatory networks (Lenski *et al.*, 2003; Edlund and Adami, 2004; Covert *et al.*, 2013), genomic architecture (Wilke *et al.*, 2001; Knibbe *et al.*, 2005, Adami, 2006; Knibbe *et al.*, 2007; Gerlee and Lundh, 2008; Batut *et al.*, 2013; Gupta *et al.*, 2016), evolution of sex (Chandler *et al.*, 2012), and evolution of cooperation (Goings *et al.*, 2004; Knoester, McKinley, and Ofria, 2007; Clune *et al.*, 2011).

Avida is the most widely used software platform for research in digital evolution (Ofria and Wilke, 2004). In Avida, self-replicating computer programs—digital organisms—evolve within a user-defined computational environment. It satisfies three essential requirements for evolution to occur: replication, heritable variation, and differential fitness. The latter arises through competition for the limited resources of memory space and central processing unit, CPU time. A digital organism in Avida consists of a sequence of code instructions—its genome—and a virtual CPU, which executes these instructions.

Some of these instructions are involved in copying an organism's genome, which is the only way the organism can pass its genetic material to future generations. To reproduce, a digital organism must copy this genome instruction by instruction into a new region of memory through a process that may lead to errors, i.e., mutations. A mutation occurs when an instruction is copied incorrectly, and is instead replaced in the offspring genome by an instruction chosen at random (with a uniform distribution) from a set of possible instructions. Some instructions are required for viability—replication—whereas others are required to complete computational operations (such as addition, multiplications, and bit-shifts), and are executed on binary numbers taken from the environment through input-output instructions encoded in the genome of the digital organism. The output of processing these numbers may equal the result of a specific Boolean logic operation, such as *NOT* and *NAND*. We call the identity of the logic operations it can perform the organism's phenotype. An organism can be rewarded for performing logic operations with virtual CPU-cycles, which speeds up the execution of its instructions. This creates an additional selective pressure (besides reducing the number of instructions required for replication) which favours those organisms in an evolving population where mutations have produced sequences of instructions in their genomes that perform logic operations. Organisms that are more successful—those that replicate faster—are more likely to spread through a population.

Natural language has been used to describe the meaning of the data resulting from performing evolution experiments using Avida. In some cases, researchers have used different terms to refer to the same entity (e.g., avidian and digital organism, or functional trait and logic operation) or the same term to refer to different entities (e.g., genome and genotype, or phenotype and logic operation). The lack of a clearly defined vocabulary, including imprecision and ambiguity, makes some biologists feel reluctant to embrace the field of digital evolution. The first step in formalizing this knowledge is to define an explicit ontology that describes unambiguously the entities relevant to this particular domain and the relations between them. In the field of digital evolution, particularly in Avida, no effort has been made yet to formalize the vocabulary beyond the documentation provided with the software.

The Ontology for Avida (OntoAvida) is open and available to everyone and provides semantics to avidaDB—a database that stores genomes (i.e., circular sequences of code instructions), transcriptomes (i.e., the code instructions that are actually executed by the CPU of an organism), and phenotypes (i.e., logic operations computed on binary numbers taken from the environment) of more than a million digital organisms. The semantic relationships between the terms commonly used in Avida are expressed in the W3C standard ontology language OWL-DL. OntoAvida is already part of the Open Biological and Biomedical Ontologies (OBO Foundry) and is currently developed by the Computational Biology Lab at the Doñana Biological Station, a research institute of the Spanish National Research Council based at Seville (Spain).

2 Ontology development.

2.1 Ontology core.

2.1.1 Classes.

OntoAvida comprises 670 classes (without including imported terms). Some of the most relevant ones are the digital analogs of genome, transcriptome and phenotype. This set of terms includes the 512 subclasses corresponding to the distinct discrete phenotypes that can be computed by a digital organism (i.e., the whole phenotype space determined by the combination of 9 logic operations that can be computed by a digital organism). Next, we categorize the main classes following the three goals that have motivated the development of OntoAvida: inference, data provenance, and reproducibility (Figure 1).

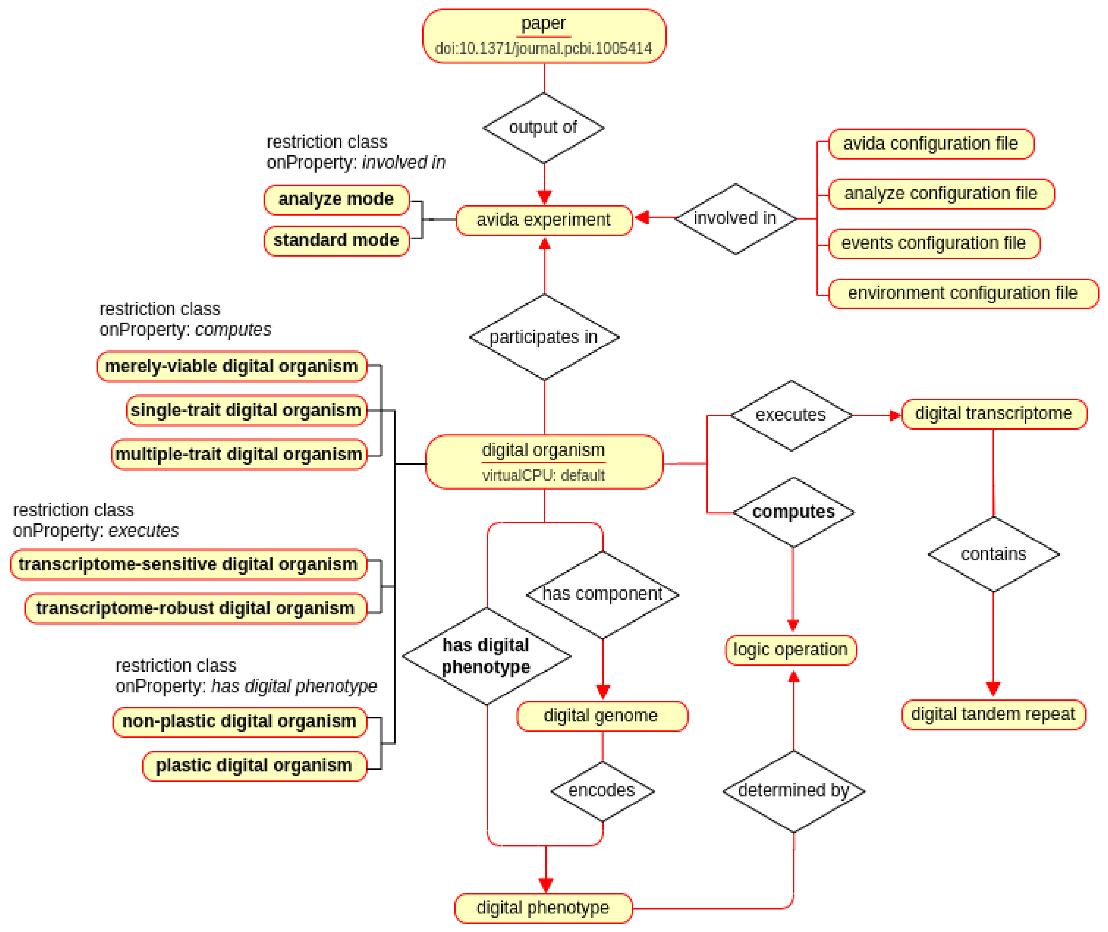


Figure 1: **Subset of the ontology showing inference, provenance, and reproducibility.** Classes and object properties are represented by rectangle and diamond symbols, respectively. The name of the inferred classes and properties are highlighted in bold face. Red arrows link classes connected by object properties, and black lines connect classes with their subclasses. Subclasses of the `digital organism` class are inferred based on restrictions applied on the properties `computes`, `executes`, and `has phenotype` (e.g., a `merely-viable digital organism` is a digital organism that does not compute any logic operation). Object properties are inferred as chain axioms (e.g., `computes` results from the combination of the properties `has component`, `encodes`, and `determined by`). We trace the provenance of the data stored in the database by indentifying the digital organisms that `participate in` an `avida experiment` reported in a scientific `paper`. In order to facilitate reproducibility in the results obtained from an `avida experiment`, we store the different configuration files associated to a particular experiment (e.g., `analyze configuration file`) as instances of their corresponding classes.

Inferring.

Besides `host` and `parasite digital organisms`, 6 subclasses—organized in groups of disjoint classes—of the `digital organism` class are inferred from data:

- `merely viable digital organism`: a digital organism that does not compute any logic operation (i.e., it can only produce an offpring).
- `single-trait digital organism`: a digital organism that computes a single logic operation.
- `plastic digital organism`: a digital organism whose genome encodes distinct phenotypes in different environments.
- `non-plastic digital organism`: a digital organism whose genome encodes the same phenotype in all environments, respectively.
- `transcriptome-robust digital organism`: a digital organism that executes the same transcriptome in all environments.
- `transcriptome-sensitive digital organism`: a digital organism that executes distinct transcriptomes in different environments.

Inferrencing is performed using restrictions on the key object properties described in the next section: `computes`, `executes`, and `encodes` (used to infer the object property `has phenotype`).

Provenance.

Provenance is an essencial requirement for building a semantic database because it contains information on the source from where the data stored in the database avidaDB come from. In OntoAvida, it involves three main classes:

- `digital organism`: a self-replicating computer program that mutates and evolves within a user-defined computational environment.

- `avida experiment`: an experiment carried out in Avida using digital organisms.

- `paper` as a specific class of `publication`: an article reporting original research, published in a peer-reviewed journal.

A digital organism can `participate in` or be `formed as result of` an `avida experiment`, depending on whether it already existed in the database or arised for the first time in a particular evolution experiment, respectively. In both cases, the experiment is reported and communicated to the scientific community in natural language mainly as a research `paper`, which is identified by the datatype `doi` (i.e., a character string used as a permanent identifier for a digital object, in a format controlled by the International DOI Foundation).

Reproducibility.

When an evolution experiment is performed in Avida, anyone should be able to replicate the experiment and have access to the data.

2.1.2 Object properties.

A core set of 10 object properties have been added in the current version (without including imported terms). This set includes properties on ecological relations such as host-parasite interactions. Key properties such as `computes`, `encodes` and `executes` depend on the computational environment experienced by a digital organism (i.e., the seed used for starting the pseudo-random number generator). For example, the environment may modify the phenotype encoded by the genome of a digital organism every time an input-output instruction code is executed. Since this instruction code takes the content of the BX register of a digital organism and outputs it, checking it for any logic operations that may have been computed on the two 32-bit binary numbers stored in its input buffers, the phenotype of a digital organism depends on the content of the BX register when an input-output instruction code is executed, and this content depends initially—and later on, every time an input-output instruction code is executed—on the environment. Then, although the same genome could execute the same sequence of instruction codes in different environments, their BX registers might contain different binary numbers and hence, the input-output instruction code would output different binary numbers that might not be the result of computing the same logic operation. Therefore, the way the genome of a digital organism encodes a specific phenotype in a particular environment is implemented through the use of containers. A container is an RDF resource used to represent collections (`https://www.w3.org/TR/rdf-schema/#ch_seq`). Specifically we use the contained `rdf:Seq` because it preserves the order of each item stored in the container (e.g., `rdf:_1`, `rdf:_2`, ...)—representing the environment or value of the seed—that are instances of the class `rdfs:ContainerMembershipProperty` (see an example of use by running a SPARQL query in the next section).

- `computes`: a relation between a digital organism and a logic operation, in which the digital organism performs the logic operation by executing the instruction codes harbored in its genome.

- `encodes`: a relation between the genome and the phenotype of a digital organism, in which the genome contains information that is used to produce the phenotype.

- `executes`: a relation between a digital organism and its transcriptome, in which the instruction codes harbored in its genome are executed to produce the transcriptome.

- `mutant of`: a relation between two digital organisms where their genomes differ in a single instruction code.

2.1.3 Datatype properties.

Only 16 datatype properties are included at this time (without including imported terms), but many more will be introduced in a near future. Since `viable` (i.e., the ability of a digital organism to produce an offspring able to replicate by executing its genome) and `genome length executed` (i.e., the number of instruction codes—out of the total number of instruction codes comprising a digital organism's genome—that are executed by a digital organism during the replication process) depend on the environment experienced by a digital organism (i.e., the seed used for starting the pseudo-random number generator), they are also implemented through the use of containers.

- `genome instruction sequence`: a genome instruction sequence is a linear string of letters representing the instruction codes that make up the genome of a digital organism.

- `transcriptome instruction sequence`: a transcriptome instruction sequence is a linear string of letters representing the instruction codes that make up the transcriptome executed by a digital organism.

- `viable`: the ability of a digital organism to produce an offspring able to replicate by executing its genome.

2.2 Ontology workflow.

We have developed OntoAvida following the principles set by the Open Biological and Biomedical Ontologies (OBO) Foundry (Smith *et al.*, 2007), which are clearly aligned with the FAIR principles (i.e,. shared data should be Findable, Accessible, Interoperable, and Reproducible). Currently, OntoAvida is listed in the OBO registry (`http://obofoundry.org`) after passing the validation checks performed by the `ROBOT` software suite (Jackson *et al.*, 2021). We used `ROBOT` commands (Jackson *et al.*, 2019) to automatize the process of developing OntoAvida (Figure 2). Next, we describe this process step by step.

2.2.1 Selecting terms from external ontologies to reuse them.

We identified the terms that can be reused from existing external ontologies, instead of creating new ones. When a term from our ontology was defined in more than one external ontology, we selected the ontology listed in the OBO registry because OntoAvida is intended to be part of an interoperable ecosystem with reuse of shared terms and relations (ref). We have reused classes from the following OBO ontologies: FlyBase controlled vocabulary (FBcv), Sex, Gender, and Sexual Orientation (GSSO) ontology, The Statistical Methods Ontology (STATO), and NCI Thesaurus OBO Edition (NCIT). All object properties reused from external ontologies come from the Relation Ontology (RO). Before extracting these terms and relations, we used a shell script that CURLs the external ontologies from their source URIs to download their latest versions. Then, we used the Syntactic Locality Module Extractor (SLME) algorithm from ROBOT to `extract` the terms as fix-point nested modules (STAR). We finally removed unwanted terms and annotations from the imported modules using `remove` and `filter`, and performed a quality control check on the extracted modules using `report`.

2.2.2 Integrating new terms proposed by contributors.

Contributors can propose new terms by adding them in template files (one for classes, another for object properties, and a third one for datatype properties). We converted the template files into OWL modules using `template`. Then, we annotated the modules

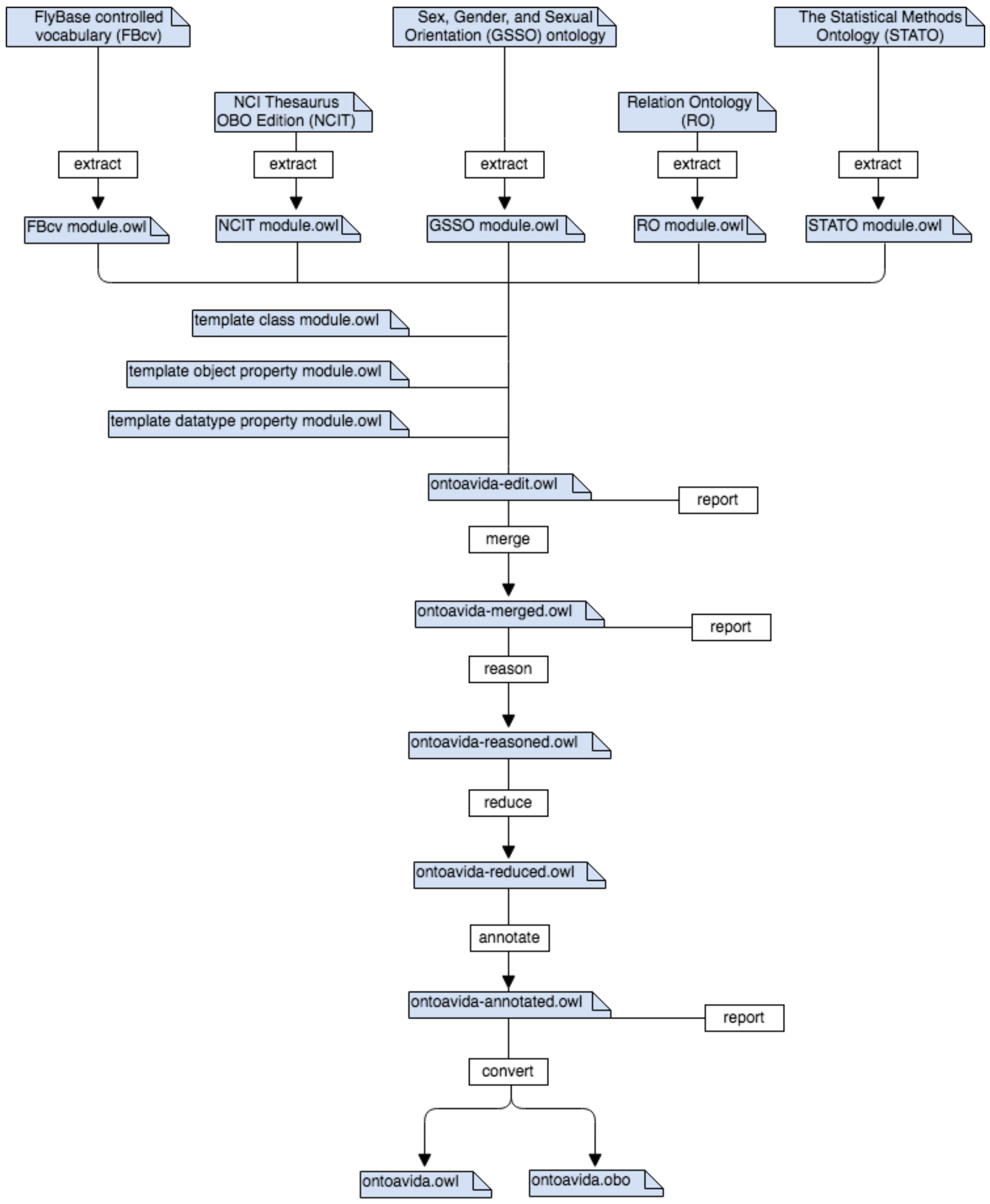


Figure 2: **Ontology workflow.** We automatized the development of the ontology using the following `ROBOT` pipeline (from top to bottom): selecting terms from external ontologies to reuse them (`extract`); integrating new terms proposed by contributors (`template`); merging imported and template modules with the core ontology (`merge`); checking the logical consistency of the ontology (`reason`, `reduce`, and `annotate`); and releasing the ontology (`convert`).

using `annotate`, and performed a quality control check on the annotated template modules using `report`.

2.2.3 Merging imported and template modules with the core ontology.

The core OntoAvida ontology was built using Protégé (Musen, 2015). We used `merge` to combine the imported modules (step 2.1), the template modules (step 2.2) and the core ontology that contains the novel terms and relations edited in Protégé. We then performed a quality control check on the merged ontology using `report`.

2.2.4 Checking the logical consistency of the ontology.

We checked the logical consistency of the merged ontology using the following `ROBOT` commands: `reason` to perform an automatic classification of terms that involves asserting all inferred superclasses, `relax` to relax Equivalence Axioms to weaker SubClassOf axioms, and finally `reduce` to remove any redundant axioms introduced by the `relax` step. Then, we updated annotations before releasing the ontology (e.g., dated version IRI) using `annotate`, and validate the OWL-DL profile using `validate-profile`.

2.2.5 Releasing the ontology.

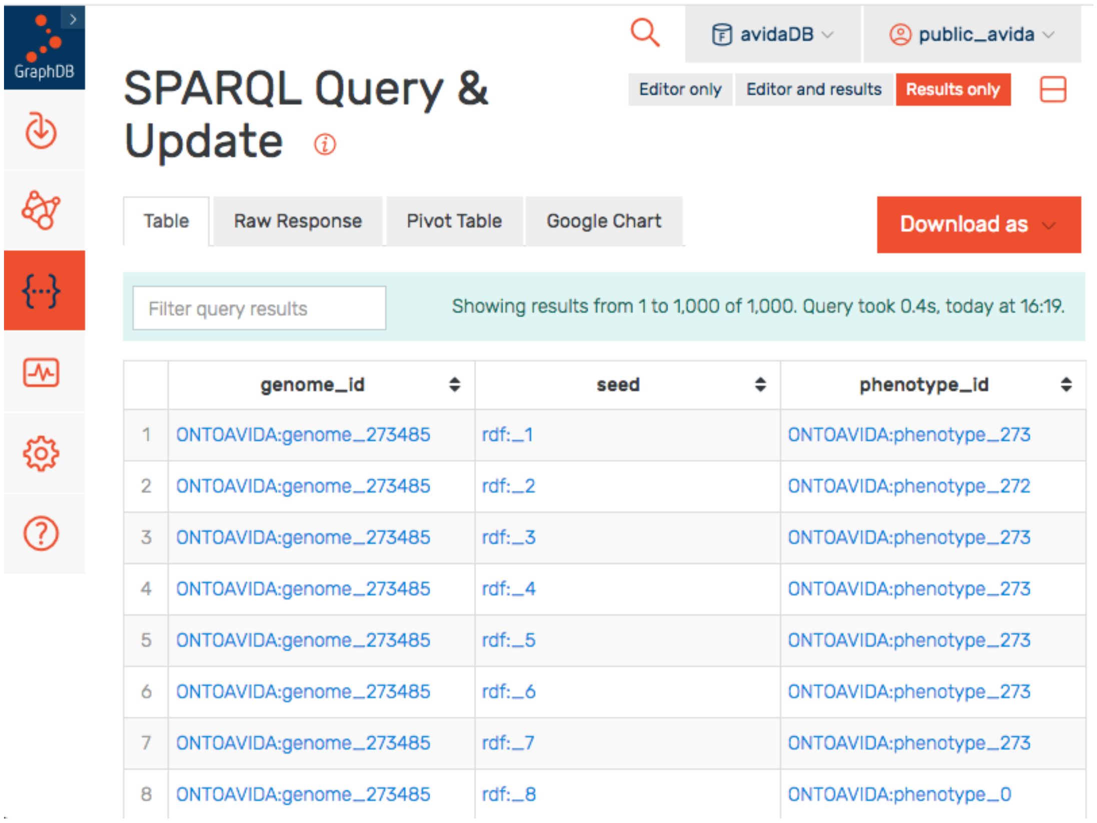
We used `verify` to create a list of terms (i.e., reporting the new terms added to the previous release of the ontology). We also converted the OWL annotated ontology to OBO (a format widely used in life science related ontologies) using `convert`. Finally, we renamed the latest version of the ontology as OWL and OBO files to stamp the date and placed them in the `release` folder of the GitLab repository.

3 Querying avidaDB.

We take advantage of the phenotypic plasticity of the digital organisms (i.e., the capability of the genome of a digital organism to encode different phenotypes in distinct computational environments) to illustrate the use of the containers in OntoAvida. We access the endpoint of avidaDB (`https://graphdb.fortunalab.org`) as anonymous user (i.e., username and password `public_avida`). The following SPARQL query retrieves the phenotypes encoded by the genome `#273485` in 1000 distinct environments (see Fig. 3):

```
PREFIX ONTOAVIDA: <http://purl.obolibrary.org/obo/ONTOAVIDA_>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>
PREFIX rdf: <http://www.w3.org/1999/02/22-rdf-syntax-ns#>
SELECT ?genome_id ?seed ?phenotype_id
WHERE {
    ?genome_id ONTOAVIDA:00001198 ?phenotype_seq .
    ?phenotype_seq ?seed ?phenotype_id .
    ?seed rdf:type rdfs:ContainerMembershipProperty
    FILTER(?genome_id = ONTOAVIDA:genome_273485)
}
```

The term `ONTOAVIDA:00001198` (`encodes seq`) represents the relation between the genome of a digital organism and the container storing the phenotypes encoded by the genome in different environments (`encodes at seed`, being `seed` the integer used for starting the pseudo-random number generator). The object of the first triple of the `WHERE` clause (`?phenotype_seq`) is the container storing the phenotypes encoded by the genome of a digital organism in each environment. The triple `?phenotype_seq ?seed ?phenotype_id` obtains the members of the container, where `?seed` takes values `rdf:_1, rdf:_2, ...,` and are instances of the class `rdfs:ContainerMembershipProperty`. The value `rdf:_1` points at the phenotype encoded at `seed=1`. For example, the first line of the output of this query, `ONTOAVIDA:genome_273485 rdf:_1 ONTOAVIDA:phenotype_273`, means that genome `#273485` encodes phenotype `#273` at `seed=1`.



Showing results from 1 to 1,000 of 1,000. Query took 0.4s, today at 16:19.

	genome_id	seed	phenotype_id
1	ONTOAVIDA:genome_273485	rdf:_1	ONTOAVIDA:phenotype_273
2	ONTOAVIDA:genome_273485	rdf:_2	ONTOAVIDA:phenotype_272
3	ONTOAVIDA:genome_273485	rdf:_3	ONTOAVIDA:phenotype_273
4	ONTOAVIDA:genome_273485	rdf:_4	ONTOAVIDA:phenotype_273
5	ONTOAVIDA:genome_273485	rdf:_5	ONTOAVIDA:phenotype_273
6	ONTOAVIDA:genome_273485	rdf:_6	ONTOAVIDA:phenotype_273
7	ONTOAVIDA:genome_273485	rdf:_7	ONTOAVIDA:phenotype_273
8	ONTOAVIDA:genome_273485	rdf:_8	ONTOAVIDA:phenotype_0

Figure 3: **Ouput of the SPARQL query reported in the main text (first 8 lines).** The SPARQL query retrieves, from avidaDB, the phenotypes encoded by the genome `#273485` in 1000 distinct environments (from `seed=1` to `seed=1000`). The predicate of the triples, `seed`, takes values `rdf:_1, rdf:_2, ...,` which are instances of the class `rdfs:ContainerMembershipProperty`. That is, the value `rdf:_1` points at the phenotype encoded by the genome at `seed=1`. The first 8 lines of the table indicate that genome `#273485` encodes phenotype `#273` at `seed=1, seed=3, seed=4, seed=5, seed=6, and seed=7`, phenotype `#272` at `seed=2`, and phenotype `#0` (i.e., merely-viable organisms) at `seed=8`.

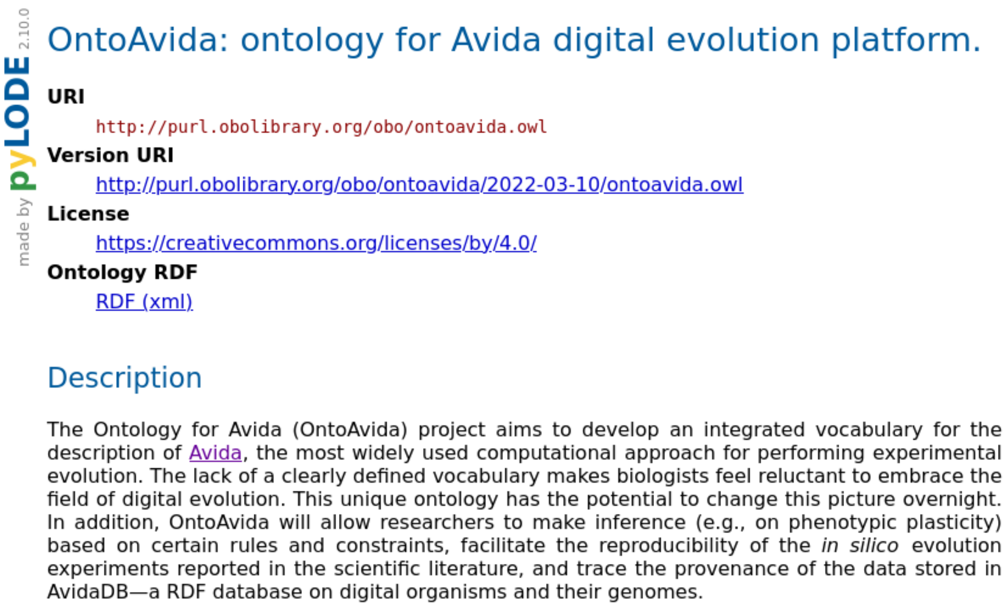
4 Community feedback and data submissions.

The OntoAvida team is expected to receive community feedback on a continual basis through individual new term requests, requests for definition, synonym or term updates.

5 Ontology availability.

OntoAvida files are available under the Creative Commons Attribution 4.0 International License (`http://creativecommons.org/licenses/by/4.0/`) which allows for the copying, redistribution and adaption of the ontology for any purpose. The ontology is available in both OBO and OWL format from the GitLab repository (`https://gitlab.com/fortunalab/ontoavida`) and can be found at `https://gitlab.com/fortunalab/ontoavida/-/blob/master/ontoavida.obo` and `https://gitlab.com/fortunalab/ontoavida/-/blob/master/ontoavida.owl`. OntoAvida OBO and OWL files are also available from the OBO Foundry (`http://www.obofoundry.org/ontology/ontoavida.html`).

We have also used pyLODE (`https://github.com/rdflib/pyLODE`) to obtain a nice visualization of OntoAvida. pyLODE is based on the OWL Documentation Environment tool (LODE), implemented in Python, and used to generate human-readable HTML documents for OWL and RDF ontologies. We have customized the original pyLODE templates (`https://gitlab.com/fortunalab/pyLODE`) to convert a scheme of OntoAvida, in a HTML file so that its classes, object properties, and datatype properties can be easily visualized. The pyLODE file of OntoAvida is available at `https://owl.fortunalab.org/ontoavida`.



OntoAvida: ontology for Avida digital evolution platform.

URI

http://purl.obolibrary.org/obo/ontoavida.owl

Version URI

http://purl.obolibrary.org/obo/ontoavida/2022-03-10/ontoavida.owl

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Ontology RDF

RDF (xml)

Description

The Ontology for Avida (OntoAvida) project aims to develop an integrated vocabulary for the description of Avida, the most widely used computational approach for performing experimental evolution. The lack of a clearly defined vocabulary makes biologists feel reluctant to embrace the field of digital evolution. This unique ontology has the potential to change this picture overnight. In addition, OntoAvida will allow researchers to make inference (e.g., on phenotypic plasticity) based on certain rules and constraints, facilitate the reproducibility of the *in silico* evolution experiments reported in the scientific literature, and trace the provenance of the data stored in AvidaDB—a RDF database on digital organisms and their genomes.

Figure 4: **pyLODE visualization of OntoAvida.** Screenshot of the HTML file generated for documenting the classes, object properties, and datatype properties of OntoAvida in an easy way.

Author contributions.

M.A.F. conceived the idea; M.A.F. and R.O. developed the ontology; E. W. contributed with XXX; M.A.F. wrote the manuscript. All authors listed have approved the work for publication.

Conflict of interest.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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