Supplementary material : Design of *Aspergillus fumigatus* collection with Meta-Obs

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1 *Aspergillus fumigatus* collection

The mycology team of University Hospital (Chrono-environment laboratory) in Besançon described in 2012 the first French case of invasive fungal infection cause by *Aspergillus fumigatus* (invasive aspergillosis) due to a resistant strain of environmental origin ([10]).

1.1 *Aspergillus fumigatus*

Aspergillus fumigatus is an ubiquitous microscopic filamentous mold responsible for a wide spectrum of respiratory pathologies, called *A. fumigatus*, with more than 10 million people in the world suffering from allergic Aspergillus pathologies, around 3 million chronic pathologies and an annual incidence of 300,000 cases of infectious pathologies ([9]). Invasive aspergillosis is the most severe form and leads to high mortality rates in patient in onco-haematology (with acute leukaemia, lymphomas) and having transplantation (haematopoietic stem cell transplants). Over the past twenty years, cases of infection involving resistant strains to triazole antifungals (molecules recommended to treat these pathologies) have been observed, compromising patient survival.

One of the pathways for the acquisition of resistance is related to the use of triazole fungicides in the environment ([13]), which are widely used in agriculture to protect cereal, vegetable, and wine crops from phytopathogenic molds, but also in the cultivation of ornamental plants and to preserve materials such as wood. These resistant strains, increasingly observed in clinical samples, are also found in different environments, more or less closely related to the use of triazole fungicides. The conditions for the appearance of these resistance mechanisms are not yet well understood (influence of stress factors, type of strains, type of reproduction), but the presence of these strains in soils is correlated with the persistent presence of triazole molecules in the environment. This emergence of resistant molds is now observed globally throughout the world. However, little is known about the distribution of triazole resistance throughout the metapopulation of *A. fumigatus*, the clonal relationship of resistant isolates and their global distribution. The modalities of dispersal of these strains from areas of high fungicide use to patient colonization are not known. It is therefore important to identify and document cases of resistant strains to elucidate the epidemiology of infections.

Thus, since the first case of infection described in Besançon, *A. fumigatus* isolated from clinical and environmental samples have been integrated into a collection, composed about 800 *A. fumigatus* that have been characterized.

The collection of *Aspergillus fumigatus* may be of interest to other research teams. For this, it is important to have a database, named DAT-Af-BASE, to centralize this information and make it available to the scientific community.

1.2 Fungal strains and characterization

The collected strains come from several clinical sources: samples from cystic fibrosis, haematology or intensive care unit patients, in the form of sputum, bronchoalveolar lavages, cerebrospinal fluid, biopsies. But many of the strains also come from the environment. On one side, the mycology team of Besançon monitors the close environment of the patients: weekly air samples have been collected from the hematology departments and corridors of the hospital (n=25 air samples per week) for 18 years ([8], [4]) and dwelling of patients at risk of infection are investigated since 2010 ([12]). On the other side, different field studies have been done in professional fields: cereals crops ([12]), sawmills ([5]), market gardens ([11]).

An identification number has been assigned to these strains and all details of isolation and characteristics and measures of analysis were filled in an excel spreadsheet (Table 1). In each case, potential resistant strains were isolated on two malt agars supplemented with 2 mg/l of itraconazole and 1 mg/1 of voriconazole. In parallel, sensitive strains are also collected to compare resistant and sensitive populations.

STRAIN box location	Sample	Sample origin	Sampling date	DNA quantity (ng/µL)	DNA extract date	*Beta-tubulin* sequencing	*Beta-tubulin* date
1E001	Patient	PMUC	04/10/2016	108	17/10/2016	Y	20/10/2016
1E002	Patient	PMUC	09/09/2015	11.9	10/06/2016	Y	13/06/2016
1E003	Patient	PMUC	13/12/2016	158	16/01/2017	Y	20/01/2017

Table 1: An extract of the original excel spreadsheet – This figure shows part of the variables measured on four strains. Dates of the manipulations are given in day/month/year format. PMUC for "Sample origine", is a code to identify department of patient's care, when sample was isolated from patient (clinical versus environmental origin). The Y means that Yes, the *Beta-tubulin* sequencing (to confirm the identification of *Aspergillus fumigatus*) has been done.

Resistance phenotypes were assessed with EUCAST (European Committee on Antimicrobial Susceptibility) microdilution method ([2]) providing minimal inhibition concentration for each tested medical antifungal and fungicide. After DNA extraction, species identification was confirmed by partial *beta-tubulin* gene sequencing ([1]) and the *cyp51A* gene and its promoter were amplified by PCR and sequenced ([6], [1]).

Short tandem repeat (STR) typing was performed for all resistant isolates and a selection of susceptible isolates using 9 highly polymorphic microsatellite markers (straf 2a, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c) ([3]). Mating type (type of sexual pairing) of strains has been also defined by PCR ([7]).

2 Design of DAT-Af-BASE database with Meta-Obs

In this section we detail the application of the Meta-Obs tool to the *Aspergillus fumigatus* collection. The first phase, the interview of the researcher, describes the data recorded in the project. The 2nd phase allows the generation of the DAT-Af-BASE database.

Whatever the research project, the order and description of the phases and steps are identical. Only the description of the data varies.

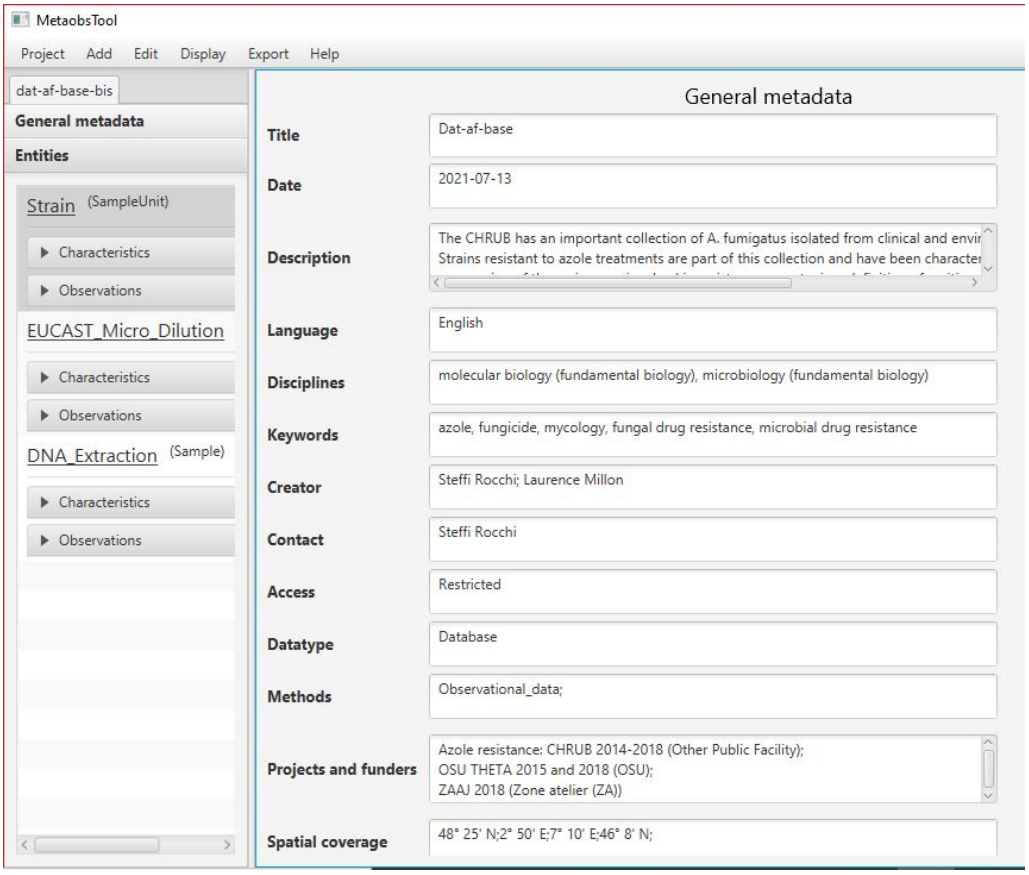

Figure 1: Screenshot of Meta-Obs tool: general metadata.

2.1 Phase 1: Interview of the researcher - Conceptual construction of the observatory

The researcher's interview is guided by the methodology, itself instantiated by the Meta-Obs tool. The questions concern: (Step 1) the description of the project (which correspond to the general metadata), then (Step 2) the entities observed and how they are collected (which will give the entities and the collection context), then (Step 3) what is measured (which corresponds to the characteristics/variables) and in which context (which corresponds to the observation context).

2.1.1 Step1: Observatory description: General metadata entry

At this step, the researcher describes the general information about the project. This information allows in particular to reference the database on data discovery portals, such as Datacite (https://search.datacite.org/) at the international level or dat@UBFC for our University (https://search-data.ubfc.fr/). Figure 1 shows the DAT-Af-BASE general metadata defined in Meta-Obs tool.

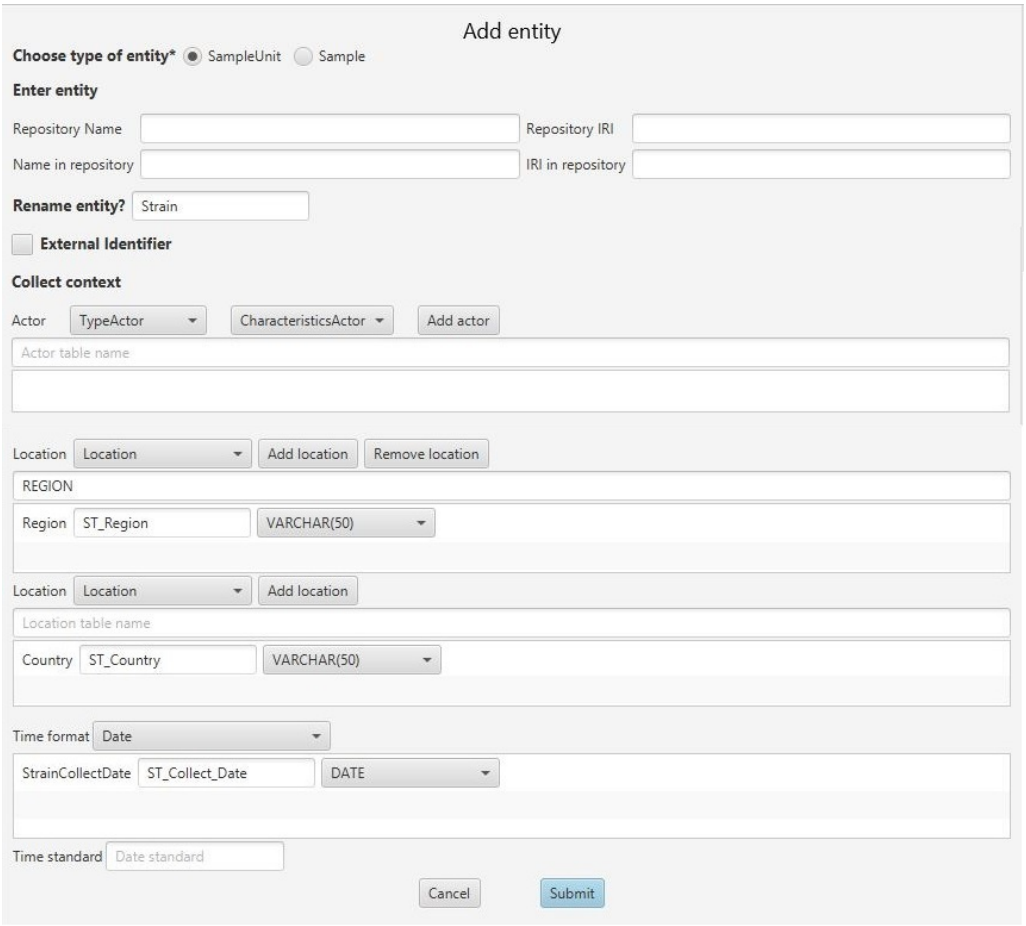

Figure 2: Description of an entity (Strain entity).

2.1.2 Step 2: Identification and description of observed entities and measured characteristics

This step allows the researcher's data to be apprehended and involves an in-depth dialogue with the researcher. In particular, it enables the process of data creation/collection to be understood.

In the case of the DAT-Af-BASE project, the data are already collected and gathered in a spreadsheet (Table 1). The definition and description of each "variable" is not explicit and must therefore be explained by the researcher. Each row of the spreadsheet contains all the information corresponding to a strain. The strain is identified as the main entity of the project and the unique sample unit of the project. Next, the difficulty is to differentiate between the samples taken from the strain and the observed characteristics.

The dates appearing in the sheet help to identify the events of collection of entities or measurements of one or more characteristics. They serve as a support for the discussion with the researcher, which enable us to identify 2 samples corresponding to culture with specific protocol.

Step 2.1: Descriptions of entities Once the entities are identified (samples and sample units), they are named, and their collection context is defined. The naming of entities must be done using terms recognized by the scientific community. It is therefore important here to use classifications or thesaurus used by this community to name these entities. It is possible to specify the repository used ("Repository Name" and "Repository IRI" in Figure 2) and the name of the entity in this repository ("Name in repository" and "IRI in repository" in Figure 2). The Figure 2 shows the description of the strain entity.

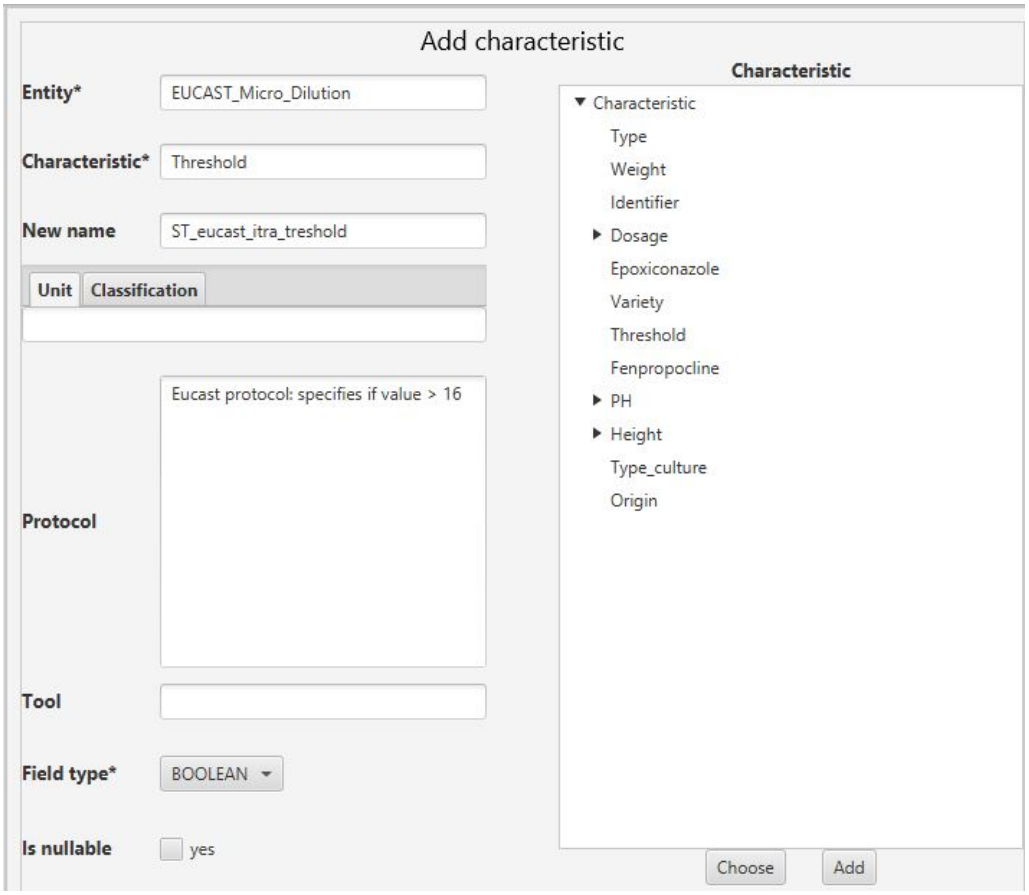

Figure 3: Description of a characteristic (ST_eucast_itra_treshold characteristic of the Eucast micro dilution entity).

Step 2.2: Characteristics measured on each entity The work carried out with the researcher makes it possible to associate each measured characteristic with an entity.

For each entity, we identify the measurements carried out on it. Each measurement is described by specifying (Figure 3):

1. Names of the characteristic: "Characteristic" is a characteristic selected or added in the "characteristics" ontology. "New name" is the name given to the characteristic in the tool.

2. Measurement information: "Protocol" is a text that describes : how the characteristic is measured or the name of a protocol recognized by the community or a link to a document describing in detail how the characteristic is measured. If known, the tool used to measure the characteristic can be filled. "Classification/Unit" specifies which classification or unit is used to express the measurement of the characteristic.

3. Useful information for the creation of the database (database field format) such as the type and size of the field used to represent the value of the measurement and if this data is required (NULL value possible or no).

The information given in point (1) and (2) are useful to prepare the reuse of data (R of FAIR). Point (3) corresponds to technical elements to implement the database.

This work realised in cooperation with the researchers allows, in particular, that data can be computer manipulated (database software for example). The characteristics are extracted from the spreadsheet (Table 1). Next, we detail the changes made on some data to make them computer manipulated.

List of characteristics

Entity name	Characteristic name	Measure	Field type	Unit or classification		Tool	Protocol	Nullable
				Unit	Classification			
Strain	ID_Strain	Identifier	VARCHAR(15)				specifies how the value of ID_Strain is defined: by concatenating the box ... String of char: N° box + location	false
Strain	ST_CRB	Identifier	VARCHAR(50)				External identifier of the biological resource centre	false
Strain	ST_Isolated	Origin	VARCHAR(4)				Enumerated type : "clinic" or "environment"	false
Strain	ST_Type	Type	VARCHAR(3)				ST_type : if origin of strain is clinical patient can be patient-hémato, patie...	false
Strain	ST_Detail_Sample	Type	VARCHAR(3)				Detail of some ST_Type	true
Strain	ST_Azole	Type	VARCHAR(3)				Phenotype of resistance : sensitive or resistant	false
Strain	ST_media_detection	Type_culture	VARCHAR(50)				Type of isolation media – Name of culture media.	false

Figure 4: List of characteristics measured on Strain.

Characteristics measured on the Strain entity are presented in the Figure 4. In the spreadsheet (Table 1), the strain was identified by the location in the well microtube freezer storage box. This identification can be problematic if a well that has become empty is reused, resulting in 2 strains having the same identifier. In order to avoid this, it was decided not to reuse the empty well and thus ensure the durability and uniqueness of the strain identifiers. ID_strain is given by the person storing the strain.

In the initial data the information concerning the origin of the strain was implicit. To define a good information system this information is made explicit. In the spreadsheet, the "type" contained a set of information that specified the strain origin, the type of origin and details about the origin. In a database, a type of information is represented by an attribute and one avoids assembling in the same attribute several pieces of information, which can later lead to query problems. In order to be able to simply processing these data by computer, we have segmented the data into three segments. Thus, the information type = "soil market garden" becomes ST_isolated = "environment", ST_type = "Market garden" and ST_detail_sample = "soil".

Characteristics measured on EUCAST_Micro_Dilution sample (Figure 5) are Minimum Inhibitory Concentrations (MIC), which indicate the sensitivity of fungal strains to a fungicide. MIC were measured for azole fungistatic molecules such as itraconazole, voriconazole, pasoconazole, tebuconazole, propiconazole and difenoconazole. In order to be able to handle the case of measurements exceeding the threshold of 16mg/liter (higher concentration tested in the reference EUCAST protocol), the ST_eucast_**_threshold attributes have been introduced. In the initial spreadsheet, the researchers noted the measurement of these characteristics on a single column in which either the concentration value or the expression ">16mg/l" could appear. In a database it is not possible to have values for the same attribute of different types. The characteristics measured here are therefore expressed by two attributes: for example, the Eucast_itraconazole characteristic is represented by the attributes ST_Eucast_itra (concentration value) and ST_Eucast_itra_threshold (boolean which indicates whether the threshold is exceeded).

Characteristics measured on DNA_Extraction sample unit are presented in Figure 6. DNA extraction was genotyped using nine microsatellites (STRAf2A, STRAf2B, STRAf2C, STRAf3A, STRAf3B, STRAf3C, STRAf4A, STRAf4B and STRAf4C). And the CYP51A gene has been sequenced to identify mutation.

List of characteristics

Entity name	Characteristic name	Measure	Field type	Unit or classification		Tool	Protocol	Nullable
				Unit	Classific...			
EUCAST_Micro_Dilution	ST_eucast_difeno	Difenoconazole	FLOAT	milligram per liter			Eucast protocol	false
EUCAST_Micro_Dilution	ST_eucast_itra	Itraconazole	FLOAT	milligram per liter			ucast protocol	false
EUCAST_Micro_Dilution	ST_eucast_posa	Posaconazole	FLOAT	milligram per liter			Eucast protocol	false
EUCAST_Micro_Dilution	ST_eucast_propi	Propiconazole	FLOAT	milligram per liter			Eucast protocol	false
EUCAST_Micro_Dilution	ST_eucast_tebu	Tebuconazole	FLOAT	milligram per liter			Eucast protocol	false
EUCAST_Micro_Dilution	ST_eucast_itra_threshold	Threshold	BOOLEAN		Boolean		Eucast protocol : specifies if value > 16	false
EUCAST_Micro_Dilution	ST_eucast_vori_threshold	Threshold	BOOLEAN				Eucast protocol : specifies if value > 16	false
EUCAST_Micro_Dilution	ST_eucast_posa_threshold	Threshold	BOOLEAN		Boolean		Eucast protocol : specifies if value > 16	false
EUCAST_Micro_Dilution	ST_eucast_tebu_threshold	Threshold	BOOLEAN		Boolean		Eucast protocol : specifies if value > 16	false
EUCAST_Micro_Dilution	ST_eucast_propi_threshold	Threshold	BOOLEAN		Boolean		Eucast protocol : specifies if value > 16	false
EUCAST_Micro_Dilution	ST_eucast_difeno_threshold	Threshold	BOOLEAN		Boolean		ucast protocol : specifies if value > 16	false
EUCAST_Micro_Dilution	ST_Eucast-vori	Voriconazole	FLOAT	milligram per liter			Eucast protocol	false

Figure 5: List of characteristics measured on EUCAST_Micro_Dilution.

List of characteristics

Entity name	Characteristic name	Measure	Field type	Unit or classification		Tool	Protocol	Nullab
				Unit	Classification			
DNA_Extracti...	ST_BTUB	Beta-tubulin ...	BOOLEAN		Boolean		Confirmed molecular identification	false
DNA_Extracti...	ST-CYP51A-Mutation	cyp51A	VARCHAR(20)				Sequencing of cyp51A gene and its promotor - List of mutations Values such as : TR34/L98H, G54E, TR46/Y121F/T289A, ...	false
DNA_Extracti...	ST_mat	mating-type ...	VARCHAR(8)		Fungal mating type gene nomencl...		Characterize mating type : MAT1-1-1 or MAT1-1-2	false
DNA_Extracti...	ST_genotype_straf2a	STRAF2a	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false
DNA_Extracti...	ST_genotype_straf2b	STRAF2b	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false
DNA_Extracti...	ST_genotype_straf2c	STRAF2c	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false
DNA_Extracti...	ST_genotype_straf3a	STRAF3a	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false
DNA_Extracti...	ST_genotype_straf3b	STRAF3b	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false
DNA_Extracti...	ST_genotype_straf3c	STRAF3c	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false
DNA_Extracti...	ST_genotype_straf4a	STRAF4a	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false
DNA_Extracti...	ST_genotype_straf4b	STRAF4b	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false
DNA_Extracti...	ST_genotype_straf4c	STRAF4c	FLOAT				Microsatellites genotyping : Number of repetitions of microsatellite	false

Figure 6: List of characteristics measured on DNA_Extraction.

Step 2.3 Definition of Observations An observation, central element of the MetaObs metamodel, groups all the characteristics measured on the same entity (sampling unit and sample) in the same observation context. Such a context makes it possible to know who carried out the measurement, when and where. Thus, for each entity, an observation groups together characteristics that have the same observation context. This step, which may seem tedious to the researcher, is essential for the design of the database model. In particular, the researcher must specify for each observation its multiplicity, i.e., whether the characteristic is measured only once or several times. Multiplicity implies different choices when designing the database.

In DAT-Af-BASE, there are 11 observations (Figure 7):

List of observations

Entity name	Observation name	Multiplicity	Date	Da...	Characteristics
Strain	Strain_Collect_Obs	1			ID_Strain,ST_Isolated,ST_Type,ST_Detail_Sample,ST_Azole,ST_media_det...
EUCAST_Micro_...	Eucast_itra_Obs	1	Eucast_itra_ObsCollectDate	Date	ST_eucast_itra_threshold,ST_eucast_itra
EUCAST_Micro_...	Eucast_vori_Obs	1	Eucast_vori_ObsCollectDate	Date	ST_eucast_vori_threshold,ST_Eucast-vori
EUCAST_Micro_...	Eucast_posa_Obs	1	Eucast_posa_ObsCollectD...	Date	ST_eucast_posa_threshold,ST_eucast_posa
EUCAST_Micro_...	Eucast_tebu_Obs	1	Eucast_tebu_ObsCollectD...	Date	ST_eucast_tebu_threshold,ST_eucast_tebu
EUCAST_Micro_...	Eucast_propi_Obs	1	Eucast_propi_ObsCollect...	Date	ST_eucast_propi_threshold,ST_eucast_propi
EUCAST_Micro_...	Eucast_difeno_Obs	1	Eucast_difeno_ObsCollect...	Date	ST_eucast_difeno_threshold,ST_eucast_difeno
DNA_Extraction	DNA_Extraction_ST_mat_Obs	1	DNA_Extraction_ST_mat_...	Date	ST_mat
DNA_Extraction	DNA_Extraction_ST_BTUB_Obs	1	DNA_Extraction_ST_BTUB...	Date	ST_BTUB
DNA_Extraction	DNA_Extraction_ST_genotype_straf_Obs	1	DNA_Extraction_ST_geno...	Date	ST_genotype_straf2a,ST_genotype_straf2b,ST_genotype_straf2c,ST_geno...
DNA_Extraction	DNA_Extraction_ST_CYP51A_Mutation_Obs	1	DNA_Extraction_ST_CYP5...	Date	ST-CYP51A-Mutation

Figure 7: List of observations in DAT-Af-BASE.

- Observation on Strain entity: the 6 characteristics of the strain entity (Figure 4) are measured in the same context. They are therefore grouped together in a single observation. These measurements are carried out only once. The Observation context is the same as the strain collection context.
- Observations on EUCAST entity: the 12 characteristics are measured on the EUCAST sample by one or more person, the EUCAST manipulators. However, the 6 MIC are not carried out on the same date. There is therefore one observation per pair (MIC and threshold), so 6 observations. Each measurement is performed only once. The observation context is different from the collection context of the sample. For each observation, only the date is informed. The measurements are carried out ex-situ, the location of observation is not relevant.
- Observations on DNA Extraction entity: the ST-Mat, STBTUB and STCYP51A-Mutation characteristics are not measured in the same observation context. They are not measured at the same date nor by the same manipulator. There is therefore one observation per observed characteristic. Each measurement is performed only once. The observation context of each observation is different from the sample collection context. It consists of the date of observation (ST_mat_date - format day/month/year). The measurements are carried out ex-situ, the place of observation is not relevant. The 9 micro-satellite characteristics measured with the genotyping protocol are measured in the same observation context. They are therefore grouped in a single observation. Each measurement is performed only once. The observation context is different from the sample collection context. It consists of the date of observation (ST_genotype_date, format: day/month/year).

2.2 Phase 2: Database script generation

When all the information describing the data has been given by the researcher, the tool can automatically generate a SQL script (Figure 8).

```
/***************** MD_Characteristics *****************/
DROP TABLE IF EXISTS `MD_Characteristics`;
CREATE TABLE `MD_Characteristics` (
`NameCharacteristic` TEXT NOT NULL,
`IRI` TEXT NOT NULL,
`IdObservation` TEXT NOT NULL,
`IdEntity` TEXT NOT NULL,
`Unit` TEXT NULL,
`Classification` TEXT NULL,
`Protocol` TEXT NULL,
`Tool` TEXT NULL
) ENGINE=InnoDB CHARSET=utf8;
LOCK TABLES `MD_Characteristics` WRITE;
INSERT INTO `MD_Characteristics` VALUES ('ID_Strain','./characteristics.owl#Identifier',
'1','1','','','specifies how the value of ID_Strain is defined:  by concatenating the
box number with the position of the strain in the box. String of char: Num box +
location','');
INSERT INTO `MD_Characteristics` VALUES ('ST_Isolated','./characteristics.owl#Origin',
'1','1','','','Enumerated type  : clinic or environment','');
```

Figure 8: Extract from the DAT-Af-BASE database creation script.

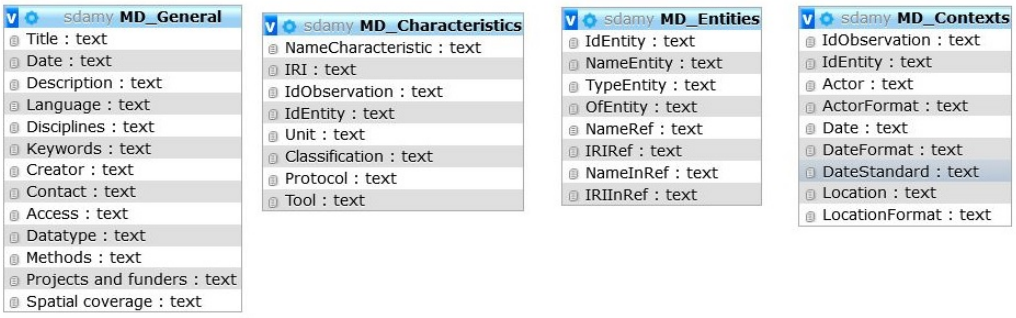

Figure 9: Relational schema of metadata tables.

The obtained script is used in MySQL DBMS (Database Management System) to create the database. This database contains two kinds of tables: metadata tables and data tables.

2.2.1 Metadata tables

Four metadata tables are generated (Figure 9):

- The MD_General table contains the Observatory MetaData information filled in step 1. This information is used to reference the database/observatory in general research data portals.
- In the MD_Entities table there is a record per entity observed in the DAT-Af-BASE observatory. It contains the Entities MetaData information filled in step 2.1
- In the table MD_Characteristics there is a record per characteristic observed in the DAT-Af-BASE observatory. It contains the Characteristics Meta Data information filled in step 2.2. The figure 10 shows two records of MD_Characteristics table.
- In the table MD_Contexts there is a record per observation. It contains the Contexts Meta Data information filled in step 2.1 and 2.3.

These metadata tables are already filled with the information retrieved during the previous steps. This information describes the database and ensures the re-use of the data and the interoperability with other databases. This information is important for obtaining FAIR (I and R) data. Whatever the data presented by the researcher, these tables have the same structure, only the data in these tables are specific to the designed database.

NameCharacter	IRI	IdObse	IdEntity	Unit	Classi	Tool	Protocol
ID_Strain	./characteristics.owl#Identifier	1	1				specifies how the value of ID_Strain is defined: ...
ST_Isolated	./characteristics.owl#Origin	1	1				Enumerated type : ?clinic? or ?environment?

Figure 10: Extract of MD_Characteristics table.

2.2.2 Data tables

To define the attributes of the data tables, the tool uses the database field formats and the names retrieved during the previous steps.

Three types of data tables are generated:

- Entity tables: For each entity one table is created. Each entity table contains attributes that represent the collection context and the values of characteristics measured only once. A record in an entity table represents one observation of one entity. In DAT-Af-BASE, three entity tables are generated (Figure 11): STRAIN, EUCAST_Micro_Dillution and DNA_Extraction. There is a link between table STRAIN and table EUCAST and a link between table STRAIN and table DNA which connect samples with sample unit.

- Information_Context tables: These tables allow the description of information about actors or locations (collection and observation contexts). In DAT-Af-BASE, 2 information_context tables are generated (Figure 11), REGION and COUNTRY that are used to describe the locations of the collections of Strains.

- Observation tables: The representation of the observations in the database depends on the multiplicity of the observation on the entity (retrieved in step 2.3). In case the multiplicity of the observation is not equal to 1 an observation table is created. In DAT-Af-BASE, no observation table is created because each observation is made only once, the observations are mapped in the entity tables.

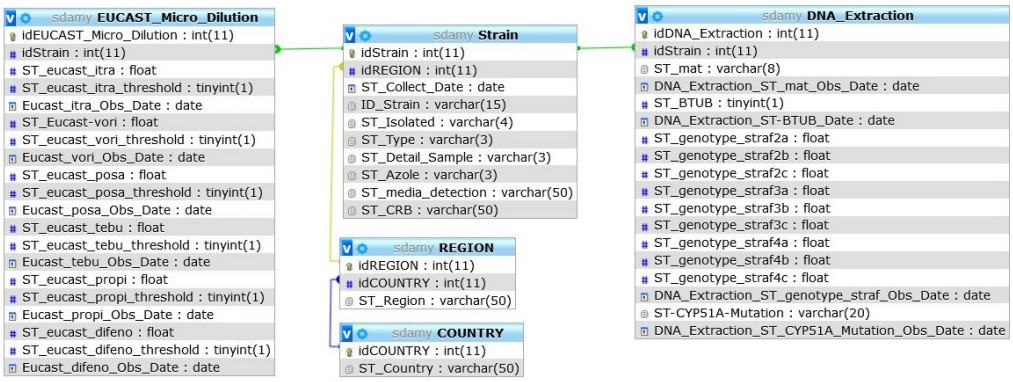

Figure 11: Relational schema of data tables

At the database generation, these tables are empty. They will be filled with the data stored in the spreadsheet.

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