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Master Thesis

A workflow for large-scale computer-aided cytology and its applications.

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Summary

Acknowledgement

Chapter 1

Introduction

Chapter 2

Object detection in large images

2.1 General problem

2.1.1 Formulation

Generic formulation of the object detection problem

2.1.2 Implementation issues

What issues an implementor could face when trying to implement object detection in large images

2.1.3 Related works

What solutions are usually presented in the litterature to solve those problems (shallow overview as this is a wide topic)

2.2 Cytology

According to the Collins dictionary, cytology is "*the study of plant and animal cells, including their structure, function and formation*" [Dic16].

2.2.1 Thyroid cytology and nodule malignancy

Nodules are growths that can develop in the thyroid. Usually, they are benign but in some cases they can be a sign of a cancer (?? give prevalence, probabilities ??). Therefore, patients presenting those nodules are subjected to a range of medical examinations. One of the most important step in those examination is the fine needle aspiration biopsy (FNAB) [BLF10]. It consists in taking a sample of tissues directly inside the nodule mass. Those takings are then stained and examined under a microscope by a physician. Especially, the nodule malignity is confirmed by the presence of some specific features such as intra-nuclear inclusions or proliferative architectural patterns. Example of stained takings are shown in Figures 2.1 and 2.2. In the former are shown cells with inclusion which are recognizable because of the typical brighter circular area inside the cell. In the latter are shown architectural patterns. Especially, proliferative patterns are shown in Figure 2.2(a) while non-proliferative ones are shown in 2.2(b).

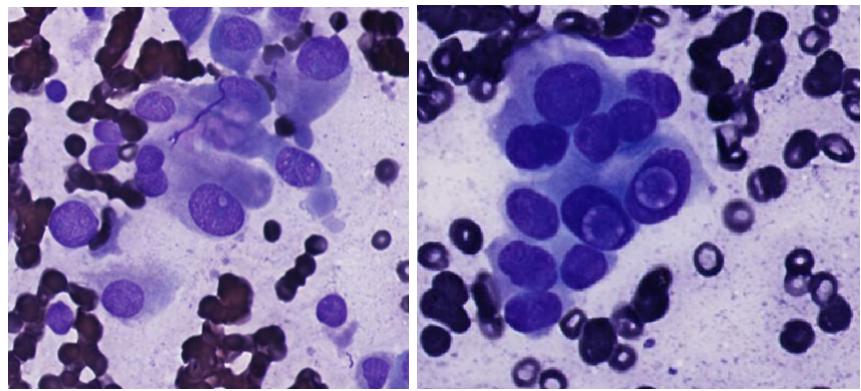
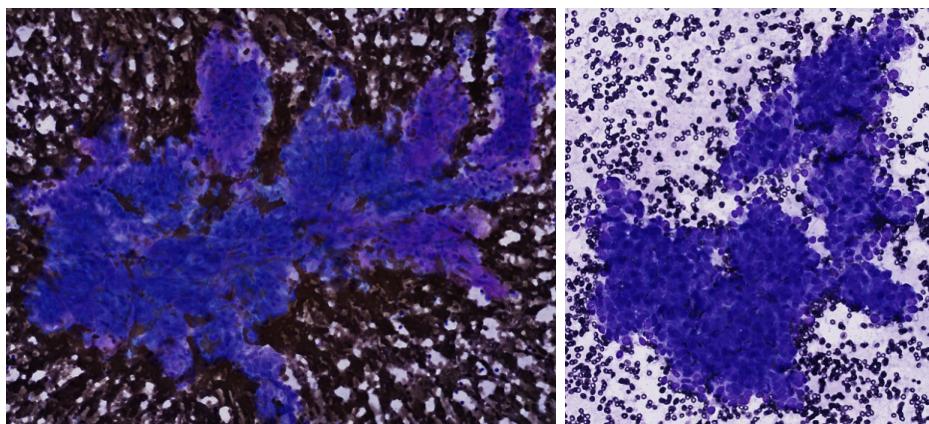
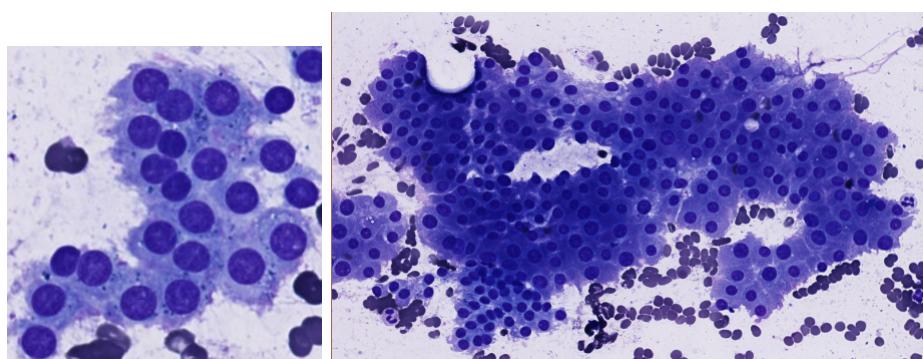


Figure 2.1: Cells with inclusion



(a) Proliferative



(b) Non-proliferative

Figure 2.2: Stained thyroid takings - architectural patterns

2.2.1.1 Cytomine

Cytomine [Mar+16] is a web-based environment enabling collaborative multi-gigapixel image analysis. Users can navigate through those images, annotate them and associate domain specific labels to the generated annotations. The platform also integrates machine learning-based image recognition algorithms that can automatically produce annotations. A reviewing system enables experts to proofread those annotations.

2.2.1.2 Dataset

A project dedicated to nodule malignancy detection was created on the Cytomine platform. It contains 61 annotated images with sizes ranging from 4 gigapixels to 18 gigapixels. Those images contain a total of 5784 labelled annotations performed by experts from the ULB (?? ref ??). Those labels (or terms) link the annotation to cytological objects related to the nodule malignancy problem. The terms made available on Cytomine are organized in an ontology which is divided into three main subcategories:

- **Architectural patterns** : includes proliferative and non-proliferative patterns but also an intermediate class for patterns which present minor signs of proliferation.
- **Nuclear features** : includes cells with inclusion, normal cells and some additional cell-related terms
- **Others** : includes artefacts, background but also poly nuclear cells, red blood cells,...

The complete ontology can be found in Appendix B. Among those available terms, the ones that matter the most in the context of nodule malignancy detection are the cells with inclusion and the proliferative architectural patterns (major or with minor sign). Those terms represent the positive classes of the problem. The distributions of terms are given in Figure 2.3. Those histograms highlight that a significant number of annotations have been made with the terms of interest. Moreover, the number of annotations is relatively balanced for those terms. While they are balanced taken alone, a problem arises when the terms are grouped. For instance, in the binary problem of determining whether a cell contains an inclusion or not, the positive class might be the term *Cell with inclusion* while the negative class might contain the all the other terms from the cell subcategory (and possibly terms from the others subcategory). While being sound, this distribution of terms in both classes results in an imbalance which can be problematic when applying machine learning classification algorithms. The classes distribution for this example problem are given in Figure 2.4.

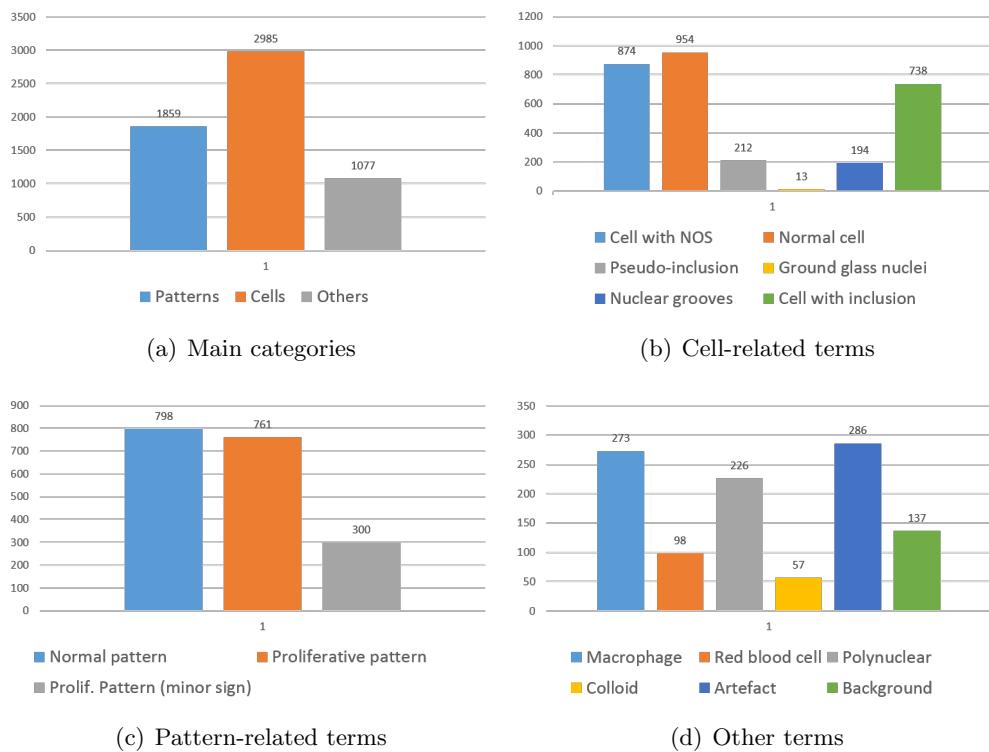


Figure 2.3: Terms of the thyroid ontology - annotation counts histograms

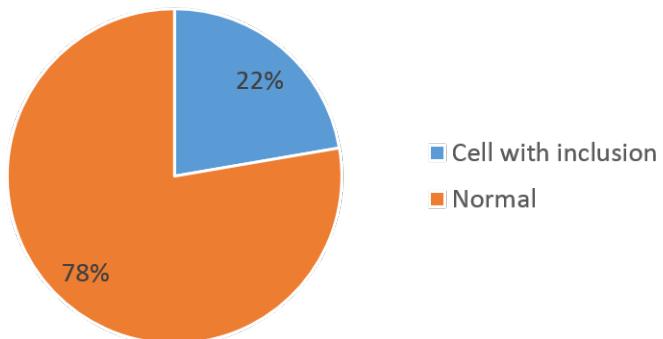


Figure 2.4: Cell inclusion detection problem. Terms in positive class: cell with inclusion. Terms in negative class: normal cells, pseudo inclusion, ground glass nuclei, nuclear grooves, red blood cells and poly-nuclear.

Chapter 3

A generic workflow : Segment Locate Dispatch Classify

In this chapter, a generic workflow for solving problems of objects detection and classification in images is presented. This workflow was first imagined by ?? JM Begon in 2015 ?? as a generalization of the work on thyroid nodule malignancy detection made by Antoine Deblire in [Deb13]. In the context of his master thesis, he had implemented a processing workflow for detecting cells with inclusion and proliferative architectural patterns (see ?? (thyroid)) in digitized thyroid puncture slides. The cells and architectural patterns were detected by segmenting the images and then classified using machine learning. As explained in the Section ?? (thyroid), some patterns could themselves contain cells with inclusion. Therefore, the author implemented a second processing workflow to detect those cells which also relied on a segmentation algorithm to isolate cells in patterns and then used machine learning to assess their malignity. From those workflows, a common pattern emerged: performing detection using a segmentation algorithm and then classifying the detected objects using machine learning.

In 2015, ?? JM Begon ?? developed a first version of a generic workflow based on this pattern and gave it the name *Segment-Locate-Dispatch-Classify* (SLDC). Unfortunately, this implementation suffered from some drawbacks which made it hard to reuse in other contexts. The workflow was therefore re-worked in the context of this master thesis.

In Section 3.1, the workflow is introduced and formalized. Especially, the various steps are detailed and then combined into an algorithm which is gradually improved to reach an acceptable level of genericity. In Section 3.2, the actual implementation of the workflow, so-called *framework*, made in the context of the master thesis is presented (?? lien GitHub ??). First are explained the reasons why the previous implementation was replaced by a new one. The new framework is then presented starting with its requirements as well as a justification for the choice of Python as the implementation language. The software architecture is then broken down and the purpose of each package and important class are explained. Section 3.2.5 presents the developments made for testing the various components of the framework. Finally, the last section illustrates the usage of the framework for solving a toy problem.

3.1 Principle

3.1.1 Algorithm

The workflow is a meta-algorithm¹ that detects and classifies objects contained in images. Particularly, given as input a two-dimensional² image \mathcal{I} from the set of all possible images I , it is expected to output the information about the objects of interest contained in this image. Those information include the shape of the object, its location as well as a classification label. Formally, the workflow can be seen as an operator \mathcal{W} :

Definition 1. Let \mathcal{W} be an operator such that

$$\mathcal{W}(\cdot) : I \rightarrow R^N \mid \mathcal{I} \mapsto \{(o_1, C_1), \dots, (o_N, C_N)\}, N \in \mathbb{N}_0 \quad (3.1)$$

where N is the number of objects of interest in \mathcal{I} and (o_i, C_i) is a result tuple belonging to the set R of all possible results tuples. The first element of this tuple, o_i , is a representation of the information (shape and location) about the i^{th} object of interest found in \mathcal{I} and the second, C_i , its classification label.

It is worth noting that genericity is of the essence. That is, the meta-algorithm should be able to solve the widest possible range of object detection and classification problems. Moreover, as explained in Section 3, it should produce those outputs using image segmentation and machine learning. As far as the segmentation is concerned, genericity is usually hard to obtain because of the high variability of images across different problems. In order to ensure that the workflow remains generic enough, a particular segmentation procedure is not imposed to the implementer who is expected to provide one that suits the problem. The same goes for the classification models used for predicting the labels of the objects.

In the subsequent sections, some additional operators are defined and used to build the \mathcal{W} operator. First, a basic version of the algorithm is presented and then refined in order to achieve an acceptable level of genericity.

3.1.2 Additional operators

Segmentation is the first operation applied to the image. This step of the algorithm is where the detection is actually carried out:

Definition 2. Let \mathcal{S} be the **segment** operator:

$$\mathcal{S}(\cdot) : I \rightarrow B \mid \mathcal{I} \mapsto \mathcal{B} \quad (3.2)$$

It is applied to an image $\mathcal{I} \in I$ and produces a binary mask $\mathcal{B} \in B$ with B being the set of all possible binary masks. The pixel b_{ij} of \mathcal{B} is 1 if the pixel p_{ij} of \mathcal{I} is located in an object of interest, otherwise it is 0.

While the segmented image theoretically contains the necessary information about the detected objects (i.e. shape and position in the image), the format of this information is inconvenient to query mostly because it is embedded into the binary mask and a single object cannot be trivially extracted. An intermediate step that would convert this information into a more convenient format is therefore needed. This format should encode both the shape of the object and its position in the image. It appears that polygons match this specification.

¹In this context, a meta-algorithm is an algorithm that coordinates the execution of other algorithms.

²A third dimension can be dedicated to the images channel (i.e. 3 channels for RGB images, 4 channels for RGBA images).

Definition 3. Let \mathcal{L} be the **location** operator. It is applied to a binary mask and produces a set of polygons encoding the shapes and positions of every object in the image. Formally:

$$\mathcal{L}(\cdot) : B \rightarrow H^N \mid \mathcal{B} \mapsto \{P_1, \dots, P_N\}, N \in \mathbb{N}_0 \quad (3.3)$$

where \mathcal{B} is a binary mask as defined in Definition 2, N is the number of objects of interest in \mathcal{B} and P_i is the polygon representing the geometrical contour of the i^{th} object in \mathcal{B} . This polygon belongs to the set H of all possible polygons.

The final step of the workflow is the object classification and is performed by a classifier which is passed a representation of the object (e.g. image, geometrical information,...) and produces a classification label. In this theory, there is no restriction about the nature or representation of the objects processed by the classifiers.

Definition 4. Let \mathcal{T} be the **classifier** operator. It is applied to an object of interest and produces a classification label. Formally:

$$\mathcal{T}(\cdot) : O \rightarrow L \mid o \mapsto C \quad (3.4)$$

where O is the set of all possible objects ($o \in O$) and L , the set of all possible classification labels ($C \in L$).

Definition 5. Let \mathcal{T}^* be an extension of \mathcal{T} which is given a set of objects and produces labels for all of them. Formally:

$$\mathcal{T}^*(\cdot) : O^N \rightarrow L^N \mid \{o_1, \dots, o_N\} \mapsto \{\mathcal{T}(o_1), \dots, \mathcal{T}(o_N)\}, N \in \mathbb{N}_0 \quad (3.5)$$

3.1.3 Single segmentation, single classifier

The most simple construction of \mathcal{W} would be the composition of the operators defined in Section 3.1.2. Particularly, the compositions $\mathcal{S} \circ \mathcal{L}$ and $\mathcal{S} \circ \mathcal{L} \circ \mathcal{T}^*$ would respectively produce the polygons representing the objects and their labels. This construction is summarized in Algorithm 1:

Algorithm 1. Construction of \mathcal{W} using one segmentation and one classifier:

1. Return $\langle (\mathcal{S} \circ \mathcal{L})(\mathcal{I}), (\mathcal{S} \circ \mathcal{L} \circ \mathcal{T}^*)(\mathcal{I}) \rangle$

As explained in Section 3.1.1, the definition of \mathcal{S} and \mathcal{T}^* would be left at the implementer's hands. As far as the \mathcal{L} operator is concerned, it could be imposed by the workflow without loss of genericity provided that the binary mask format is defined. Such a construction of \mathcal{W} could already solve any object detection and classification problem on image in which the labels can be predicted by a single classifier. However, in some cases, one classifier is not enough. This happen, for instance, when the image contains objects of very different nature and using several classifiers would yield better results than using a single one. An extension is therefore needed.

3.1.4 Single segmentation, several classifiers

In this attempt to construct a generic \mathcal{W} operator, the image is assumed to contain M distinct types of objects and the workflow uses M classifiers (the i^{th} classifier being noted \mathcal{T}_i with $i \in \{1, \dots, M\}$) to classify those objects. As an object should only be processed by one classifier, the workflow has to be added a new step which consists in dispatching each polygon to its most appropriate classifier.

Definition 6. Let \mathcal{D} be the dispatch operator. It is applied to a polygon and produces an integer which identifies the most appropriate classifier for processing this polygon:

$$\mathcal{D}(\cdot) : H \rightarrow \{1, \dots, M\} \quad (3.6)$$

This step being problem dependent, it is the responsibility of the implementer to define the rules used for dispatching the polygons. However, the format of these rules can be defined.

Definition 7. Let \mathcal{P} be a set of M predicates p_1, \dots, p_M which associate truth values to polygons:

$$p_i(\cdot) : H \rightarrow \{\text{true}, \text{false}\} \mid P \mapsto t, i \in \{1, \dots, M\} \quad (3.7)$$

where p_i is the predicate associated with the i^{th} classifier. The polygon P is dispatched to a classifier \mathcal{T}_i if p_i associates true to this polygon. To avoid dispatching an object to several classifiers, the predicates should verify the following property:

$$p_i = \text{true} \Leftrightarrow p_j = \text{false}, \forall j \neq i \quad (3.8)$$

Given this format, the \mathcal{D} operator can be trivially constructed as it returns i if p_i is true. The algorithm resulting from this construction of \mathcal{W} starts the same way as in Section 3.1.3: the image is applied the segment and locate operators. Then, the resulting polygons are dispatched and classified to produce the labels. The resulting algorithm is summarized in Algorithm 2. Figure 3.1 illustrates Algorithm 2 with a workflow that has two classifiers. The first is designed to classify small objects while the second classifies bigger ones.

Even though the workflow can now handle several types of objects, there are still some particular problems that cannot be solved with Algorithm 2. In particular, this algorithm works perfectly as long as objects are not included in one another. In this case, the workflow will consider their intersection as a single object and therefore won't be able to distinguish them.

Before extending the algorithm for handling this case, it is worth noting that Algorithm 2 is completely compatible with Algorithm 1. Indeed, if there is only one classifier (i.e. $M = 1$) and the predicate p_1 always returns true, then both algorithms are exactly the same.

Algorithm 2. Construction of the \mathcal{W} operator with a single segmentation and several classifiers.

1. Apply the $\mathcal{S} \circ \mathcal{L}$ composition to the input image \mathcal{I} to extract the objects of interest as the set of polygons $S_p \leftarrow \{P_1, \dots, P_N\}$
2. Initialize the labels set $L \leftarrow \emptyset$
3. For each polygon $P \in S_p$:
 - (a) Compute the classification label $C \leftarrow \mathcal{T}_{\mathcal{D}(P)}(P)$
 - (b) Place the label in the labels set $L \leftarrow L \cup \{C\}$
4. Build and return objects and labels set $S_p \times L$.

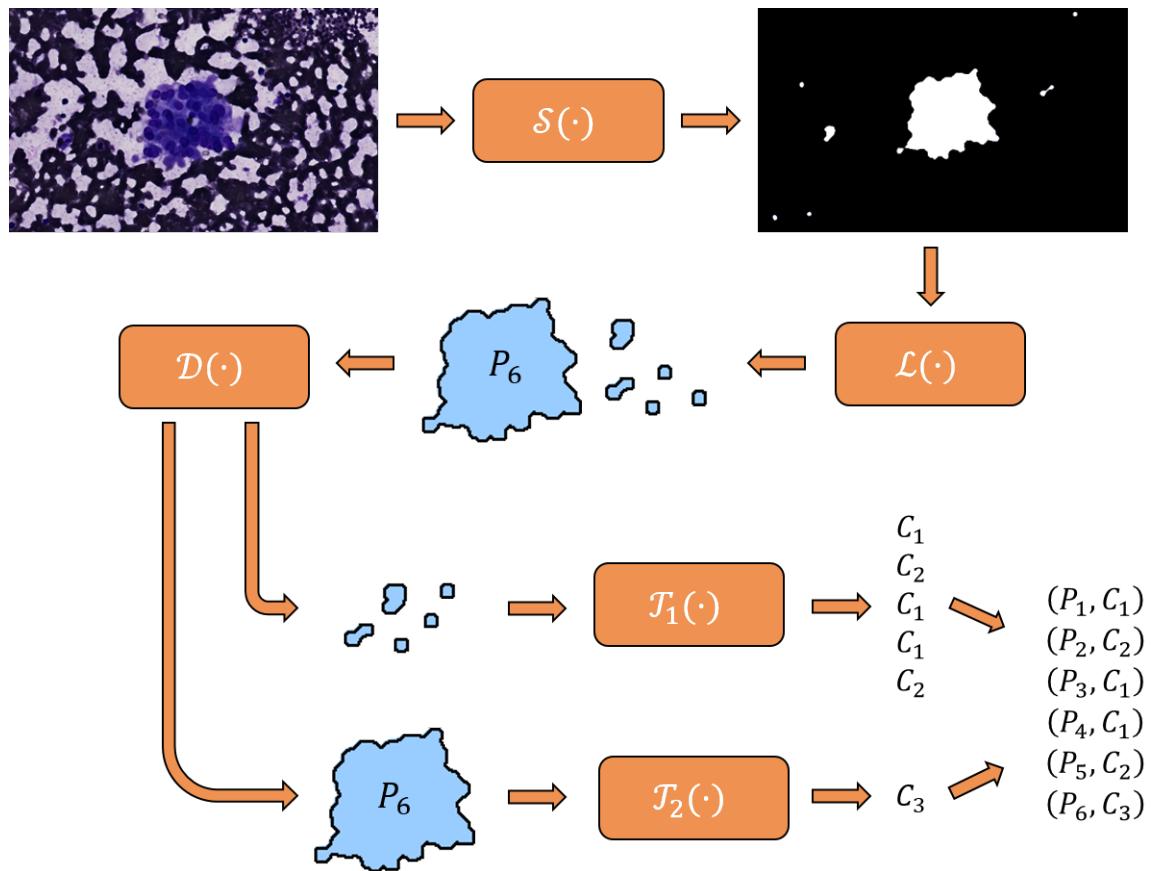


Figure 3.1: Illustration of Algorithm 2.

3.1.5 Chaining workflows

To handle the case when some objects are included in others, a solution consists in executing several instances of Algorithm 2 one after another.

Definition 8. Let $\mathcal{W}_1, \dots, \mathcal{W}_K$ be a set of K instances of Algorithm 2. Each algorithm \mathcal{W}_i has its own segmentation procedure \mathcal{S}_i and proper sets of dispatching predicates \mathcal{P}_i and classifiers $S_{\mathcal{T},i}$.

While \mathcal{W}_1 would be applied to the full image \mathcal{I} to extract all the objects of interest, $\mathcal{W}_2, \dots, \mathcal{W}_K$ would only be passed image windows containing the previously detected objects. Given those windows, they would have to detect the objects of interest included in the objects found by \mathcal{W}_1 .

Definition 9. Let $\mathcal{I}_P \in I$ be an image window extracted from image \mathcal{I} and containing the object represented by polygon P . The window is the minimum bounding box containing this polygon.

A further refinement would be to provide a way for the implementer to filter the polygons of which the windows are passed to a given workflow instance. Indeed, a given instance \mathcal{W}_i might be designed to process only a certain category of objects and therefore should not be passed windows of objects that doesn't fall in this category.

Definition 10. Let \mathcal{F} be the *filter* operator. It is given a set of polygons S_P and returns a subset S'_P of polygons:

$$\mathcal{F}(\cdot) : H^N \rightarrow H^M, N, M \in \mathbb{N}, M \geq N \quad (3.9)$$

Each instance of the workflow \mathcal{W}_i except \mathcal{W}_1 is therefore associated a filter operator \mathcal{F}_i . The resulting algorithm is given in Algorithm 3 and has now reached an acceptable level of genericity. The algorithm is illustrated in Figure 3.2.

Algorithm 3. Construction of the \mathcal{W} operator with K instances of Algorithm 2:

1. Execute the first workflow and save the results in the result set R : $R \leftarrow \mathcal{W}_1(\mathcal{I})$
2. Create the polygons set and initializes it with the polygons found from the execution of \mathcal{W}_1 : $S_P \leftarrow \{P_{1,1}, \dots, P_{1,N}\}$
3. For each $i \in \{2, \dots, K\}$:
 - (a) Extract polygons to be processed by \mathcal{W}_i : $S'_P \leftarrow \mathcal{F}_i(S_P)$
 - (b) For each polygon $P \in S'_P$:
 - i. Execute workflow \mathcal{W}_i on the image window and saves the results: $R \leftarrow R \cup \mathcal{W}_i(\mathcal{I}_P)$
 - ii. Add the extracted polygons to the polygons set: $S_P \leftarrow S_P \cup \{P_{i,1}, \dots, P_{i,M_i}\}$
4. Return the results set R

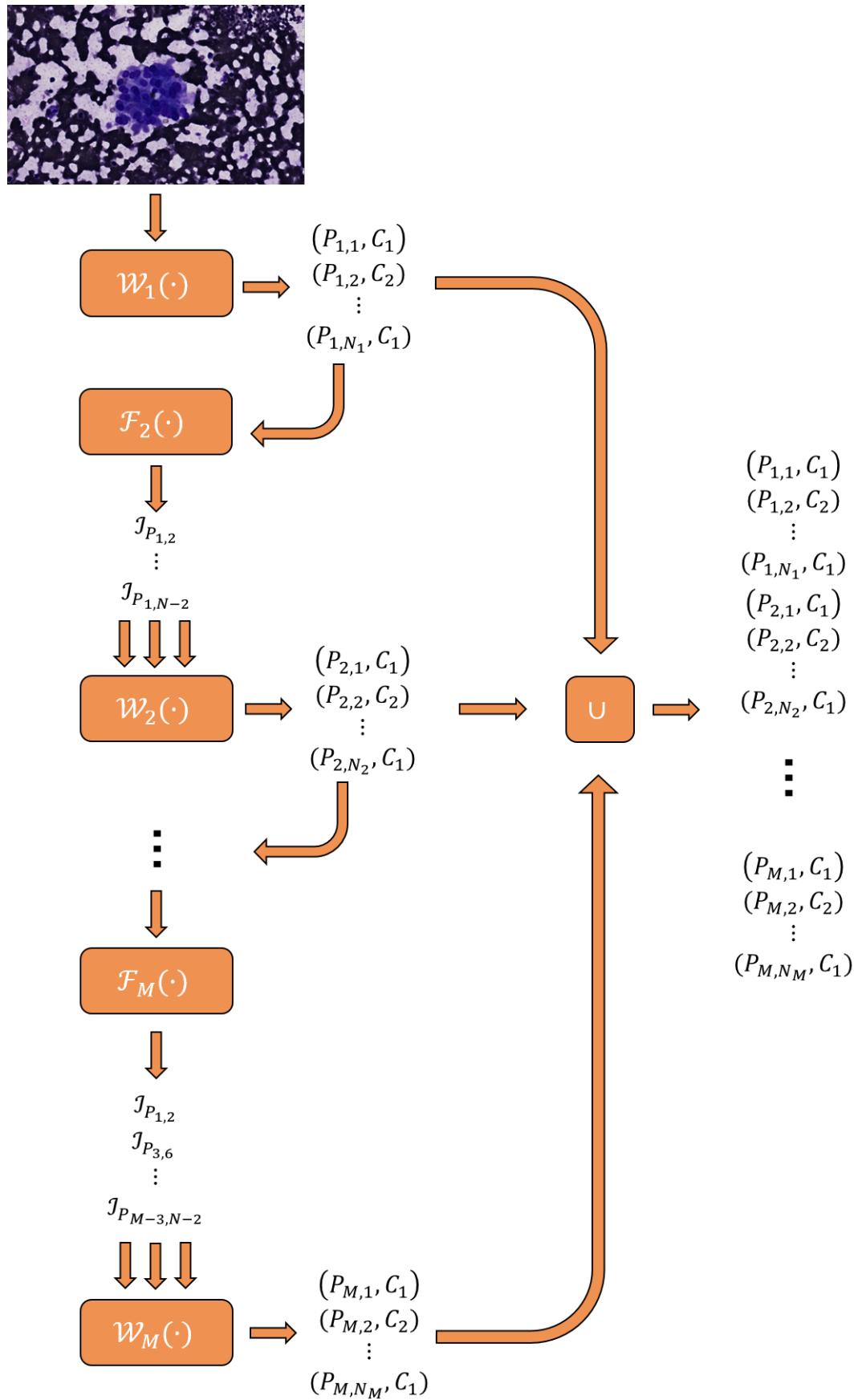


Figure 3.2: Illustration of Algorithm 3

3.2 Implementation

This section aims at presenting the implementation of the workflow formalized in Section 3.1. In Section 3.2.1, the reasons why the previous implementation was replaced by a new one are presented. Then, the requirements, design choices and architecture of the new framework³ are given in Sections 3.2.2, 3.2.3 and 3.2.4. Finally, how to apply the framework is illustrated with a toy example in Section 3.2.6. The framework discussed in this section is available on GitHub ?? at this url ??.

3.2.1 Initial implementation

As explained in this chapter’s introduction, a first version of the workflow was implemented in 2015. However, in the context of this thesis, the decision was made to re-implement it for various reasons.

A major issue was the presence of a software component called a *datastore* which had to be defined by the implementer for each distinct application of the workflow. In addition to be a dependency of almost every other class of the framework, it actually forced the implementer to define workflow execution and chaining logic himself although this logic is obviously not problem dependent and could be encapsulated. The major consequence of this design was an increased workload for the implementer to apply the framework to a custom object detection and classification problem. Moreover, the datastore being tightly coupled with other classes, it made writing automated tests quite difficult. Reproducing bugs was even harder because the replication implied to restore the datastore state which was not trivial.

Another issue with the previous implementation was its too high level of genericity. Most of the components of the framework were defined as abstract classes and interfaces to be derived or implemented by the implementer. This made the framework hardly understandable and difficult to apply as he had to define more than just problem dependent components. In some cases, some implementations were provided but they only increased the complexity of the framework. Indeed, it was not clear whether those classes could be used directly or whether the implementer should provide his own classes.

Another final critical point was the lack of robustness. Especially, when applied to the thyroid case where images were fetched using HTTP requests, any network error would exit the program, leading to the loss of all collected data.

All in all, it was decided to re-implement the framework to get rid of the flawed parts of the design while keeping the good parts. The philosophy behind the new framework is illustrated through a set of requirements in Section 3.2.2.

3.2.2 Requirements

The main requirements for the framework are listed hereafter.

Genericity As for the algorithm, the framework should be able to solve the widest possible range of object detection and classification problems in any context. This property has more implication in the case of the framework design than for the algorithm design, especially when it comes to fixing the representation of the various involved data types (i.e. image, polygon,...).

³In this section, the term *workflow* will refer to the algorithm while *framework* will refer to the implementation.

Efficiency While the framework has no control over the efficiency of the algorithms defined by the implementer (i.e. segmentation or classification procedures), the coordination of those algorithms should not induce a significant overhead in the overall execution.

Large images While large images handling was irrelevant at the algorithm design stage, it becomes critical at this point. To remain generic, the framework should not make any assumption about the size of the images to be processed. Especially, a whole image should not be assumed to fit into memory.

Robustness The framework should be robust to errors. That is, a single error should not interrupt the whole execution. For instance, if the framework executes a set of independent computations and one of them fails, it should only be stopped if this failure is unrecoverable and affects all the other computations. Otherwise, the failure should be reported and those others computations should execute until completion.

Transparency The framework should provide a built-in way to communicate its progress, the duration of each step as well as the errors it encounters with the user. The level of verbosity of this communication tool should be adjustable. Moreover, all the relevant information generated by the framework should be made available to the implementer in a structured and convenient way.

Parallelism Whenever possible the framework should take advantage of parallelism to reduce its execution time but the implementer should be given a way to switch to sequential execution. Moreover, the implementer should be able to adjust the level of parallelism (i.e. the number of available processors).

Ease of use The work of the implementer should be kept as minimal as possible. He should only have to define the logic of the workflow components that are problem dependent : image format, segmentation, dispatching rules, classifiers,...

3.2.3 Language

The first choice occurring in the development of an existing algorithm is obviously the language in which it will be implemented. As far as the workflow is concerned, the chosen language was Python. Indeed, this language provides a simple, accessible and complete environment for solving the kind of problems addressed by the framework and would therefore contribute to the overall ease of use the framework.

First of all, the language has many features which allows developers to quickly come up with solutions to problems. Especially, it is strongly and dynamically typed, multi-paradigm (imperative, functional, object oriented,...), interactive (it can be used in an interactive console), interpreted and garbage-collected. It also supports usual data structures such as lists, arrays, dictionaries and sets natively and provides operations for manipulating them in a concise way.

In addition to its built-in features, Python has become a great language for scientific computing as it has been augmented with excellent open source libraries over the years. First, the SciPy ecosystem which includes the SciPy [Oli07] and NumPy [VCV11] libraries. The first is a collection of numerical algorithms and domain-specific toolboxes (signal processing, optimization, statistics,...). The second is a fundamental package for numerical computations which provides an efficient representation of multi-dimensional

arrays and operations on them. Built on top of the SciPy ecosystem comes Scikit-Learn [Ped+11], a library that provides simple, efficient and reusable tools for data mining and machine learning. Image processing is not outdone with a Python binding for the huge OpenCV library [Bra00]. Two alternatives are scikit-image [Wal+14] which is built on top of the SciPy ecosystem or the Pillow library [Cla16]. All of them provide a collection of well-known image processing algorithms. Another useful library is Shapely [Gil13] which provides a representation for geometrical objects (e.g. polygons) and operations on them.

Python was also chosen because the workflow was implemented to be integrated with Cytomine (see Section ??). Particularly, the final goal was the detection and classification of objects in images stored on Cytomine servers. As those images and their metadata are exposed through an API interfaced by a Python client, it was essential that the workflow could use this client to communicate with the back-end. As the Cytomine client was implemented in the version 2.7.11 of Python, this version was also used for developing the framework.

3.2.4 Software architecture

The framework was organized as a Python library of which the root package was called `sldc`.

3.2.4.1 Image representation

The image representation design is a critical point of the framework architecture. Indeed, on the one hand, it should be abstract enough so that implementers can apply the workflow on images in any format. On the other hand, it should provide access to a concrete representation available to the framework because some steps need to access this representation to extract some information. For instance, location is one such step as it processes a binary mask to extract polygons.

The representation should also provide a way of extracting sub-windows from an image. The need for this feature is twofold. First, it is needed by the workflow (see Definition 9). Then, it could be used to address the large images handling requirement and to overcome the fact that a whole image is not assumed to fit into memory. The idea is to split the image into smaller chunks called tiles which could be loaded into memory and processed one after another. Especially, the tiles would be applied the first part of the workflow, that is segmentation and location. As the polygons of each tile are extracted independently, it might occur that a single object of interest which spreads over several tiles ends up being splitted into several polygons. To make sure there is a one to one relationship between a polygon and an object of interest, an additional step must be added to the workflow before the dispatching and would consist in merging the polygons representing a same object. This step is detailed in Section 3.2.4.4.

The abstract image representation and related classes were implemented into the `sldc.image` package presented in the UML diagram shown in Figure 3.3.

The `Image` class is the abstract image representation mentioned above. It provides three abstract methods for checking image dimensions (width, height and number of channels) and a fourth one, `np_image`, which should implement the conversion between the implementer's custom image format and the concrete format mentioned above. NumPy multi-dimensional arrays were chosen to be this concrete representation. In addition to the inherent advantage of using the NumPy library, this choice was also motivated by the fact that those arrays are compatible with the various image processing libraries presented in Section 3.2.3.

An image window is materialized by the `ImageWindow` class of which the design is based on the decorator pattern. It stores information about the position and size of the window as well as a reference to the parent image. Especially, location and size are respectively represented by coordinates of the first top left pixel included in the window (coordinates are referenced to the top left corner of the parent image) and by the window width and height. As an image window instance provides a level of indirection on top of another image, some methods are provided to fetch this base image as well as the absolute offset⁴.

A tile is also represented by a class named `Tile` which extends `ImageWindow` and augment it with an integer identifier field. As tiles can potentially be derived, a `TileBuilder` interface was developed. As suggested by the name, a class implementing this interface is responsible for building specific tile objects. This structure is actually an application of the factory method pattern which has the advantage of allowing the framework to build specific tiles objects defined by the implementer while remaining unaware of the construction logic of those objects. The implementer that would derive the `Tile` class to implement a custom loading procedure in `np_image` is advised in the documentation to raise an `TileExtractionError` exception if the loading fails. This allows the rest of the framework to handle loading failure and therefore increase its robustness.

Finally, to make it easier to iterate over the tiles of an image two classes were developed : `TileTopology` and `TileTopologyIterator`. The first is responsible for dividing an image into a set of overlapping tiles. The overlap allows the merging procedure to be simpler as polygons corresponding to a same object will have a geometrical intersection.

The tile topology is fully defined with three parameters: the tile maximum width, w_m , and height, h_m , and the number of pixels that overlap, o_p . The tile topology object also associates unique increasing identifiers to the tiles. An example topology with its resulting tiles and identifiers is shown in Figure 3.4. As soon as the `TileTopology` object is built, it can be queried using those identifiers for building tile objects or for fetching topology information such as one tile's neighbours identifiers. While this organization goes off from the object oriented philosophy a bit, it allows all operations provided by the tile topology object to be $\mathcal{O}(1)$ (see Appendix A). It goes without saying that the overlap parameter should be set carefully because it induces some additional computations. Indeed, some parts of the image will be segmented several times as they are present on more than one tile.

The second class, `TileTopologyIterator`, is an application of the iterator design pattern as its name suggests. It can be created either from a tile topology or directly from a subclass of `Image`. It allows to iterate over the tiles defined by a tile topology. The implementation of this iterator is straightforward. It simply iterates over the tile identifiers and pass them to the corresponding tile topology to build the tiles.

3.2.4.2 Segmentation

As explained in Section 3.1.3, the segmentation is not fixed by the framework and the implementer is expected to provide its own implementation. To represent this constraint in the framework, a `Segmenter` interface was defined in package `sldc.segmenter`. It provides a single method, `segment`, which receives a NumPy representation of the image and is expected to return another NumPy array storing the binary mask marking the objects of interest contained in this image. The binary mask however doesn't conform strictly to Definition 2 as pixels belonging to an object of interest are marked with the

⁴The absolute offset is the offset of the window referenced to the base image's top left pixel. It is different from the image window offset if its parent image is also an image window.

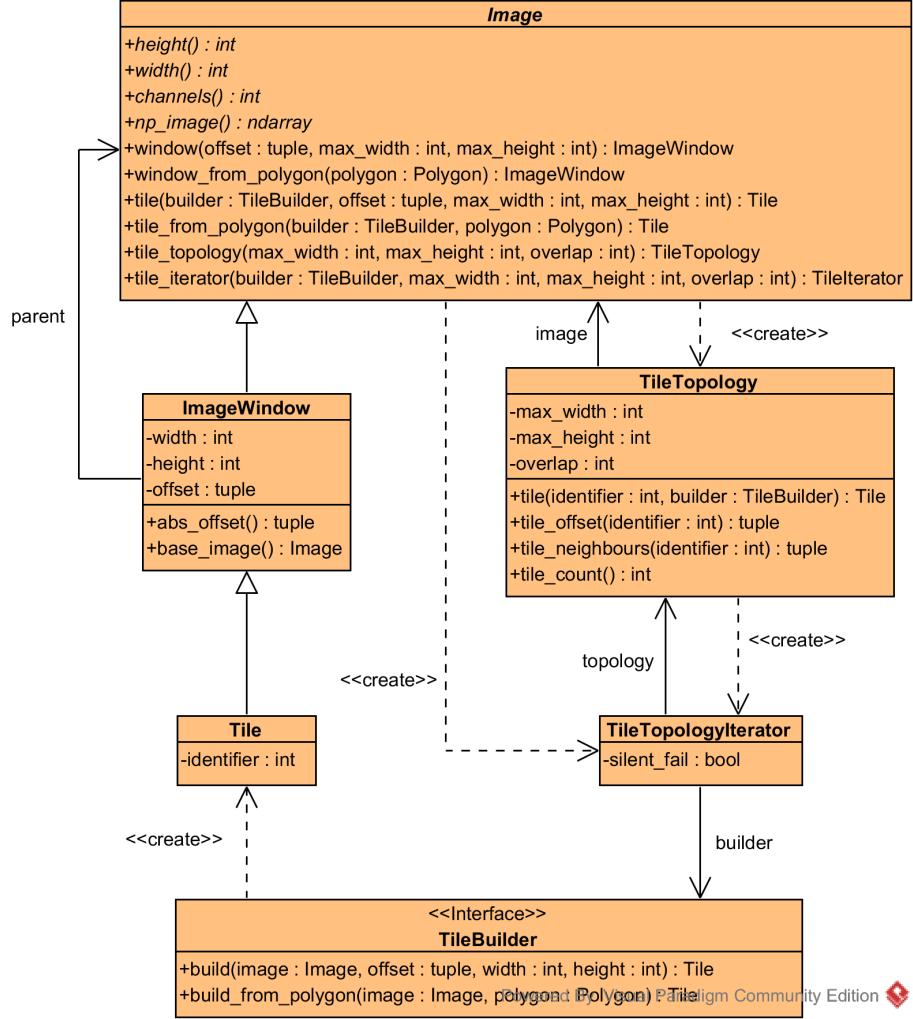


Figure 3.3: Image representation classes - package `sldc.image`

integer value 255 (which corresponds to white in the grayscale color space) instead of 1. The `Segmenter` interface is Shown in Figure 3.5.

3.2.4.3 Location

As presented in Definition 3, the location procedure extracts polygons representing the geometrical contours of the objects of interest from a binary mask. The implementation of this operation was done in the single method, `locate`, of a class called `Locator` (in package `sldc.locator`). This method takes as parameter the binary mask represented by a NumPy array and returns the expected set of polygons as Shapely `Polygon` objects.

As stated in Section 3.1.3, this operation can be fixed by the framework without loss of generality. This is made possible by the choice of representation for the method's inputs and outputs. As far as the implementation is concerned, it was largely inspired from another implementation taken from the Cytomine codebase. It uses the `findContours` procedure of the OpenCV library to extract the geometrical information of the objects as a list of coordinates. The implementation provided with the framework has two small additions compared to the Cytomine one. The first is the conversion of those coordinates into `Polygon` objects and the second is an optional translation that can be applied to

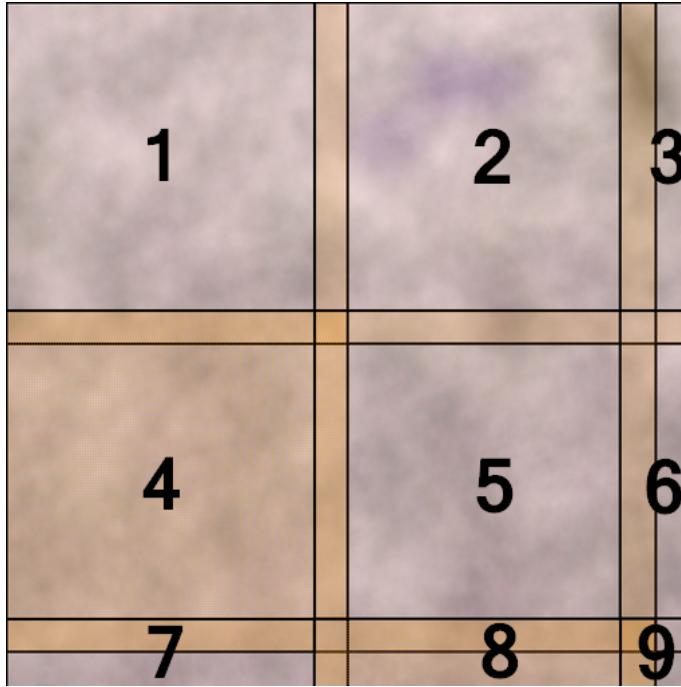


Figure 3.4: A tile topology applied on a 512×512 image (parameters: $w_m = 256$, $h_m = 256$ and $o_p = 25$). The numbers are the tile identifiers.

those polygons. This second modification is needed because of the image division in tiles. Indeed, by default, the location algorithm constructs polygons referenced to the top-left pixel of the binary mask passed to `locate`. Yet, the polygons are expected to be referenced to the full image top-left pixel. An additional parameter was therefore added to the `locate` method prototype allowing the caller to specify a translation offset to apply to the found polygons. The `Locator` class is Shown in Figure 3.5.

3.2.4.4 Merging

The need for a merging phase is a consequence of the image division in tiles and its goal is to merge distinct polygons that actually represent a same object of interest. The main idea behind the algorithm was imagined by ?? JM Begon ??. It consists in building a graph where each node corresponds to a polygon. The algorithm will then add edges between polygons which correspond to a same object. Two polygons represent a same object if the distance between them (i.e. minimum distance between one point of each polygon) is less than a certain tolerance threshold. Generating the final polygons is as simple as finding all the connected components of this graph and computing the intersection of all the polygons in those components.

While working in some cases, the implementation made by Jean-Michel Begon could be improved. First, the interface of the class was inconvenient to use. Indeed, the tiles and their polygons had to be provided in a fixed order (i.e. increasing order of identifiers). And if they weren't, the merging would fail. Moreover, it had issues with some border cases. For instance, with small images containing few tiles. For those reasons, the algorithm was kept but was completely reimplemented to take advantage of the `TileTopology` object (which didn't exist in the previous implementation of the workflow).

The classes related to merging were defined in the package `sldc.merger`. The main

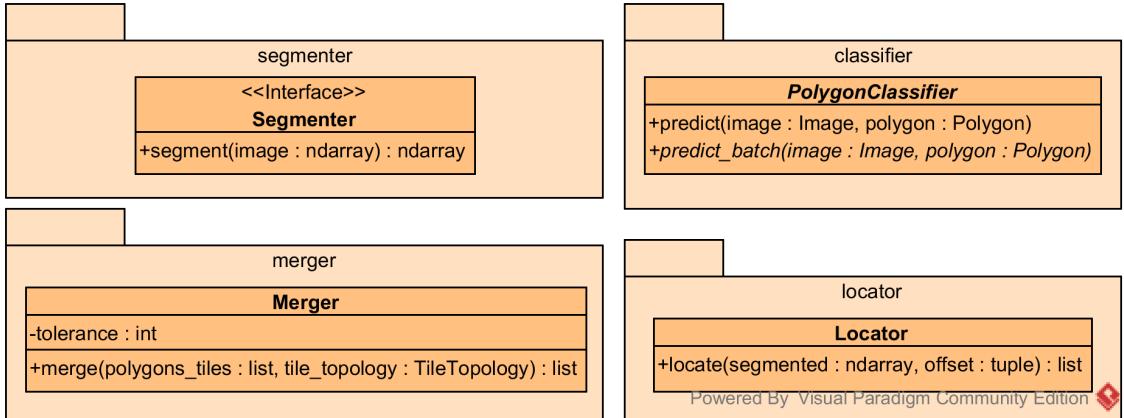


Figure 3.5: Packages `sldc.segmenter`, `sldc.locator`, `sldc.merger` and `sldc.classifier`.

logic of the algorithm was implemented in a class called `Merger`. Applying a merge is as simple as passing a tile topology as well a the tiles and associated polygons to the `merge` method which return the list of merged polygons. The `Merger` class is Shown in Figure 3.5.

3.2.4.5 Dispatching and classification

As defined in Section 3.1.4, the dispatching of polygons to classifiers is performed using predicates. Those predicates are materialized by the abstract class `DispatchingRule` in package `sldc.dispatcher`. The implementer can extend to define its custom dispatching logic. Especially, this is done by implementing the method `evaluate_batch` which is passed both a list of polygons to dispatch as well as the image from which they were extracted. Passing both the polygons and the image allows the implementer to define a dispatching logic based on either the polygons geometrical properties, or the polygons crops, or both.

The same philosophy was followed for classification. The implementer has to extend the abstract class `PolygonClassifier` from package `sldc.classifier` (see Figure 3.5). For the same reason as for the `evaluate_batch` method, the `predict_batch` methods takes as parameters a set of polygons and the image they were extracted from. Although only a label is produced by the classifier operator in Definition 4, an additional element is returned by the `predict_batch` method: the class probability (i.e. the probability that the predicted label is indeed the label of the object). Indeed, this information can sometimes be extracted using some classifiers (e.g. tree based methods). However, it can happen that the underlying classifier is not able to generate those probabilities. In this case, the implementer is advised to return a probability 1 for each polygon. The class `PolygonClassifier` is shown in Figure 3.5.

While the dispatching and classification logic are problem dependent, the coordination of those steps is obviously not and is implemented in class `DispatcherClassifier` (see Figure 3.6). This object must be initialized with a set of classifiers and dispatching rules. Some polygons can then be dispatched and classified by passing them to the methods `dispatch_classify` or `dispatch_classify_batch`. Especially, the first will execute the operation on a single polygon while the second allows to process a set of polygons.

To answer the transparency requirement, it is essential that all the relevant information generated by these methods can be accessed by the implementer after the execution.

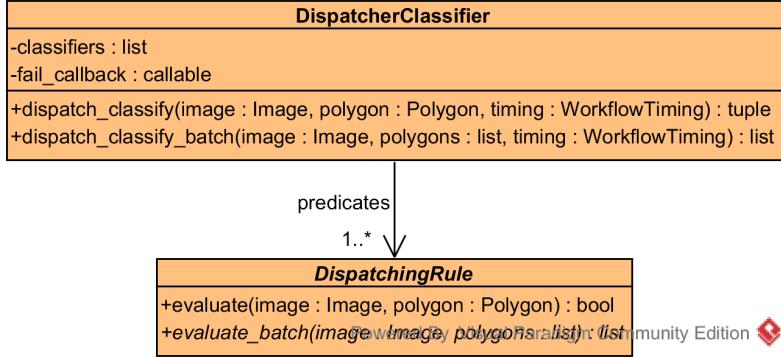


Figure 3.6: Package `sldc.dispatcher`

Those information obviously include the classification label and its associated probability but not only. Indeed, another relevant information generated is the identity of the dispatching rule which matched a polygon. In practice, this information can be used by the implementer to distinguish a same classification label returned by different classifiers. The `dispatch_classify` method therefore returns a tuple containing the label, the probability and the identifier of the dispatching rule that matched the polygon (this identifier being the index of the rule in the list passed at construction). The `dispatch_classify_batch` method returns three lists containing the same information for all the passed polygons.

In the workflow, it is assumed that one and only one dispatching predicate can be true at once. In practice, the framework should handle sets of predicates which don't verify this property. Especially, it should handle a first case when more than one rule match a polygon and a second case when no rule matches a polygon.

The first case is handled by ordering the rules and to only consider the first rule that matched. Especially, the ordering is defined by the order of the rules in the list provided by the implementer at construction.

The second case is handled with a fail callback. This function is passed the polygon that didn't match any rule and return a value or object that will be used as classification label. A default callback which always returns `None`⁵ is used if the implementer doesn't provide one. Moreover, the dispatch index associated to those unmatched polygons is -1.

3.2.4.6 Workflow

The package `sldc.workflow` contains the actual implementation of Algorithm 2, in `SLDCWorkflow` class. Instantiating this class requires three mandatory parameters: a `Segmenter` which implements the tile segmentation logic, a `DispatcherClassifier` which was initialized with custom dispatching rules and polygon classifiers and a `TileBuilder` for building the tiles of the tile topology. The workflow can then be launched on an `Image` object using the method `execute`. This method returns all the information about the objects of interest found in the image. Those information include the polygons encoding the object's shapes and locations, their predicted classes, the associated probabilities and the dispatching indexes (see Section 3.2.4.5). In order to provide a convenient access to those information, they were encapsulated into an object called `WorkflowInformation`. Especially, this class provides a way to iterate over the results, the method `results`. The UML diagram containing both the `SLDCWorkflow` and `WorkflowInformation` classes is given in 3.7.

⁵`None` is the `null` equivalent of Python.

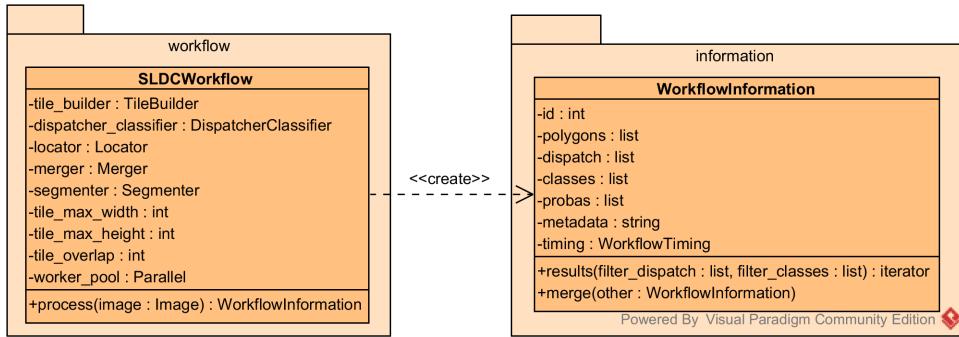


Figure 3.7: Package `sldc.workflow` and class `WorkflowInformation`

3.2.4.7 Workflow chain

To this point, the presented classes provide a way for an implementer to apply Algorithm 2. The package `sldc.chaining` allows to go one step further as it contains the necessary components for applying Algorithm 3. Especially, the class `WorkflowChain` coordinates the execution of several workflows one after another on one or more images and also handles the post processing of the generated data. Those operations are handled by different components defined hereafter. The UML diagram containing the classes of this package is shown on Figure 3.8.

The images to be processed by the workflow must be generated by an implementation of the interface `ImageProvider`. The implementer must define the image generation in the abstract method `get_images`.

The post processing of the generated data must be defined by the implementer as `PostProcessor` object. Especially, he has to implement the method `post_process` which is passed a collection of workflow information objects as well as the image from which they were generated.

As far as the workflow objects to be executed are concerned, they must be encapsulated into subclasses of `WorkflowExecutor`. This component has three main responsibilities.

The first is to generate the image windows that will actually be processed by the underlying `SLDCWorkflow` object. Particularly, those windows must be generated based on the polygons generated from the previous steps of the chain. This generation must be implemented in the `get_windows` method. This method is also the placeholder for the filtering specified in Definition 10. As far as the first workflow of the chain is concerned, its `get_windows` method should have a slightly different behavior. Indeed, in this case, the full image is yet to be processed and should be returned. In the optic to reduce the work of the implementer, a abstract subclass named `FullImageWorkflowExecutor` was defined to implement this behavior. Its `get_windows` method simply returns the image it is passed.

The second responsibility is to launch the `execute` method of the `SLDCWorkflow` object on the images generated by the executor in `get_windows` and to collect the generated workflow information objects. This is done in the `execute` method.

The last responsibility is the post-processing of the results generated by one workflow execution. This logic must be implemented in the method `after` which is passed the image window that was processed as well as the workflow information object returned by the `execute` method of `SLDCWorkflow`. An example usage of this method is the translation of polygons generated by a `SLDCWorkflow` on an image window. Indeed, in this case the polygons returned by the workflow object are reference to the window top left pixel while

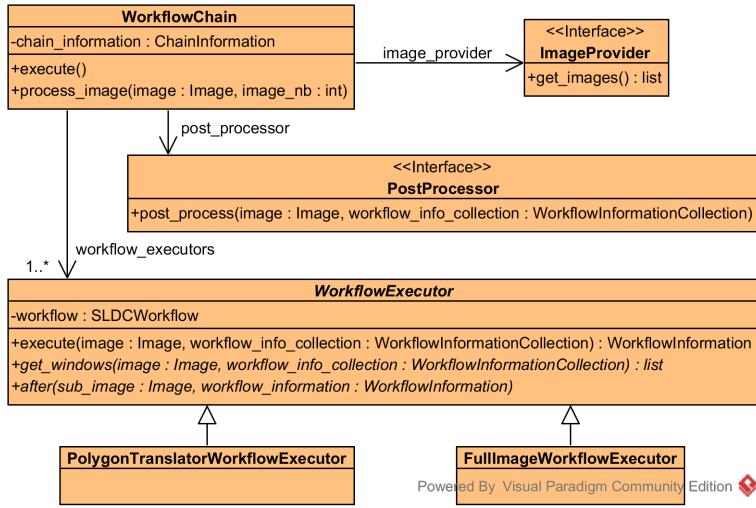


Figure 3.8: Package `sldc.chaining`

they should be referenced to the full image top left pixel. For the same reason as the `FullImageWorkflowExecutor`, a subclass of `WorkflowExecutor` was created. Its `after` method implements the translation logic.

As soon as the `ImageProvider`, `PostProcessor` and `WorkflowExecutor` objects are constructed, they should be passed to the `WorkflowChain` constructor. The chain can simply be started by calling the `execute` method.

3.2.4.8 Logger and workflow timing

To fulfill the transparency requirements, it is essential that the person who executes a workflow chain is able to monitor the progress. He should also have some insights about how the workflow performs on a given problem. For instance, how many tiles must be processed, how many polygons were found, how many polygons were dispatched,... The user should also be informed about the execution times of the various phases. In order to perform those operations two other packages were added.

Logging The first one is `sldc.logger` which provides a flexible, powerful and thread-safe logging system. Especially, it allows to log messages selecting a level verbosity among `silent`, `debug`, `info`, `warning` and `error`. The output can be controlled using a minimum level of verbosity. All messages sent below this level won't be outputted. The implementer can also choose where the messages will be printed (in a file, on the standard output,...).

The logging package is articulated around the abstract class `Logger` which holds the minimum level of verbosity and provides methods to log messages in all the defined levels of verbosity. It also implements the message formatting. Especially, the messages sent by the implementer are augmented with a prefix containing the thread id, the current date and time as well as the level of verbosity at which it was sent.

What this class doesn't define is where the formatted messages will be printed. This is the responsibility of the subclasses. Three of them are provided in the package: `StandardOutputLogger`, `FileLogger` and `SilentLogger`. The first one prints the messages into the program's standard output, the second prints them into a file while the last ignores all messages. If the implementer is not satisfied with one of those implementation, he can define himself a subclass that handle messages in a custom way.

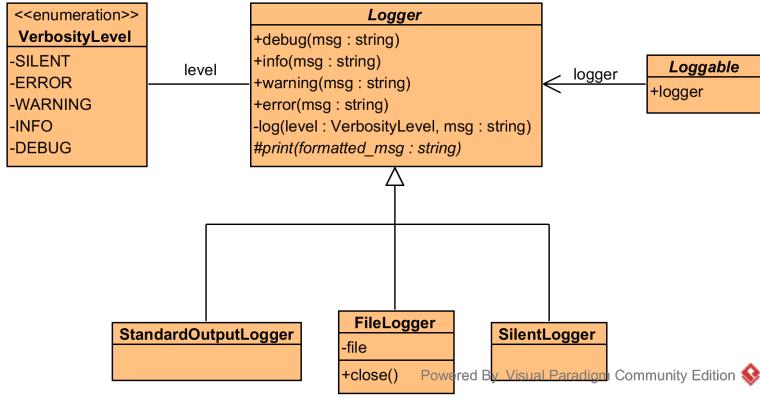


Figure 3.9: Package `sldc.logging`.

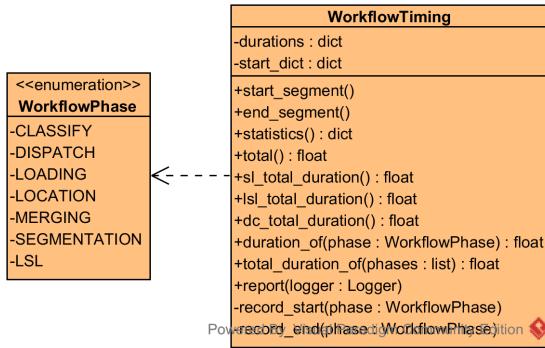


Figure 3.10: Package `sldc.timing`.

The final component of the package is an abstract class called `Loggable`. Its first goal is self documentation for the classes which extend it. Indeed, those are expected to support logging. The second goal is to provide a logger attribute for the classes which extend it. This way, they don't have to define their own.

The UML diagram of the logging package is shown in Figure 3.9.

Timing The second package, `sldc.timing`, contains the `WorkflowTiming` class which allows to record execution times of the various phases of the workflow but also to report them. The time computation is provided through some `start` and `end` methods for each phase. For instance, for recording segmentation time, the methods `start_segmentation` and `end_segmentation` are provided. The phases that can be recorded are the following: image loading, segmentation, location, merging, dispatching and classification. A last phase is actually a combination of the loading, segmentation and location phases and is called *lsl*. An additional method is needed for this combination because it can be parallelized (see Section 3.2.4.10). Recorded execution times can be extracted with a handful of methods such as `total` which computes the total recorded time for all phases, or `report` which is passed a `Logger` object and prints some statistics about the execution times. The UML diagram of this package is shown in Figure 3.10.

3.2.4.9 Builders

The package `sldc.builder` contains two classes `WorkflowBuilder` and `WorkflowChainBuilder` for making easier the construction of `SLDCWorkflow` and `WorkflowChain` objects respec-

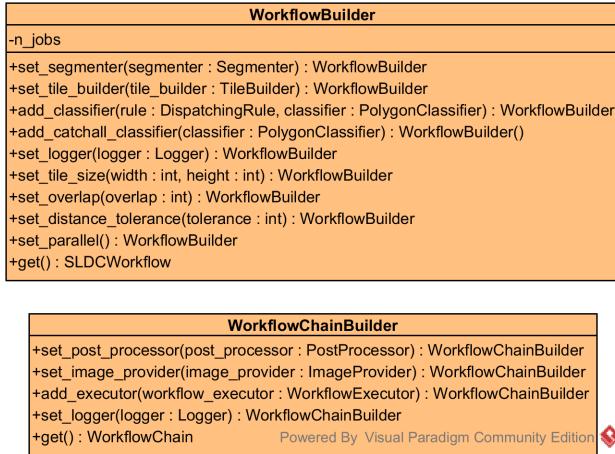


Figure 3.11: Package `sldc.builder`.

tively. Those classes provide some methods for setting the construction parameters and a `get` method for actually constructing the expected object based on the provided parameters. For instance, the `WorkflowBuilder` provides a method `set_segmenter`. The UML diagram of this package is shown in Figure 3.11.

3.2.4.10 Parallelization

As stated in the requirements, the framework should allow the user to take advantage of parallelism to reduce overall execution time. First, it is important to understand few things about parallelism in Python. The language natively provides packages for parallelizing code: `multiprocessing` and `threading`. A library called `joblib` was built on top of those packages and provides a high level interface for writing parallelized loops in a very concise way. As far as threading is concerned, some implementation of the interpreter (i.e. CPython) prevents the threads to execute concurrently because of the Global Interpreter Lock (GIL). This lock is acquired by the thread which executes and prevents the other threads to access the interpreter for executing their own code. Therefore, it is advised in the language documentation to use multiprocessing to ensure that code is effectively executed in parallel whatever the interpreter implementation. Working over several processes however has the drawback of requiring inter-process communication. Particularly, the processes must be passed the data to treat and return the generated results to the main process. This is handled by `joblib` using serialization. Especially, the elements to be processed in parallel are queued. When a process becomes available, an element is dequeued, serialized and transferred to this process. When it terminates its execution, the results are themselves serialized and returned to the main process. This organization has the drawback of triggering as many serialization and deserialization as there are objects to process. Yet, such operations induce a non-negligible overhead that can be overcome by passing batches of elements instead of single elements to the processes. Another important point is the fact that `multiprocessing` doesn't support nested parallel loops. This constraint imposes therefore at most one level of parallelism. That is, a code executing in a spawned process cannot itself spawn other processes. All these language and library specific constraints were taken into account when including the parallelism to the framework.

How the parallelism will be implemented is now known, the question yet to be answered is where it will be applied. Several steps of the algorithm can be retained as candidates

because of their highly parallelizable nature. In this case, highly parallelizable means that the parallelization can be done without any synchronization mechanisms except the ones provided by `joblib`. Typically, this is the case for operations which imply several independent computations. At the workflow level, the candidates steps are tiles segmentation and location, polygons dispatching and polygons classification. At the chaining level, the processing of the images generated by the `ImageProvider` is another candidate.

Whereas applying parallelism at the chaining level is very easy, the idea was abandoned for the following reasons: it would prevent the parallelization at the workflow level (because of the nested parallel loops issue) and it can be done manually by the implementer. Indeed, he just has to launch its program one time on each image to obtain the same result.

At the workflow level, both dispatching and classification parallelization were dropped because it would require more work and the need was less obvious than for segmentation and location. Indeed, it was assumed that the segmentation procedure provided by the implementer was likely to be computationally expensive. So the advantage resulting from this parallelization might be greater than for the two other operations.

The parallelization itself is handled in the `SLDCWorkflow` class. In order to reuse the same pool of processes for every call of the `execute` method, this pool must be passed to the constructor of the workflow object as a `joblib.Parallel` object. In order to provide more feedback about progress to the user in the sequential case, two implementations of segmentation and location were made. Therefore, the workflow switches to one or another implementation according to the number of jobs specified by the user. The parallel implementation first splits the tiles in batches and then submits them to the various processes using the pool. After that, it aggregates the returned data. Especially, in addition to the found polygons, each process returns a `WorkflowTiming` object containing the loading, segmentation and location times it recorded when processing its assigned tiles. Those objects are merged with the `WorkflowTiming` to be returned by the `execute` method.

To avoid any concurrency problems, all classes of the framework were developed to be thread safe. This was done by making those classes immutable whenever possible or by avoiding to use shared resource. The only classes which couldn't verify this rule are `WorkflowTiming`, `StandardOutputLogger` and `FileLogger`. The timing objects can indeed be updated with new time recordings after their creation. The loggers by printing log messages access shared resources (e.g. standard output, files,...). To prevent any problem, the `Logger` was added a lock object to synchronize the call to the `_print` abstract method which actually implements the submission of the message to the resource.

3.2.5 Testing

In order to ensure that the various components of the framework are working as expected in some predefined conditions and to prevent those components to be broken by further refactoring, some tests were written using the `unittest` package of Python. Those tests can also be found on GitHub in the folder `tests`.

The tests were focused on components containing actual logic, that is, the classes `Locator`, `DispatcherClassifier`, `Merger` and `TileTopology`. The workflow construction and execution was also tested on two use cases. The first is presented in Section 3.2.6 and the second consists in finding a big white circle in a image with black background. Finally, there are fifteen tests and they yield a code coverage of 72 %.

3.2.6 Toy example

Now that the implementation was presented and detailed, this section aims at highlighting how easy it is to apply the framework to solve a problem. The problem in question is very simple and consists in finding grey and white squares and circles within a greyscale image with a black background (see in Figure 3.12). In addition to locate the shapes, the algorithm should return the information about whether a shape is a circle or a square and also return a label indicating its color (grey or white).

To apply the workflow philosophy, the implementer should first encapsulate its image custom format in a class extending `Image`. For this example, a simple NumPy array can be used to represent the image. The definition of the image class is given in Listing 3.1. The next component to be defined is the segmentation algorithm that will actually detects the objects. In this case, this algorithm can be implemented using a simple thresholding (every pixel of which the value is greater than 0 belongs to an object). This logic should be defined in a class implementing the `Segmenter` interface. The definition of this class is shown in Listing 3.4. Thanks to the usage of NumPy arrays, the implementation of the segmentation is really concise.

The next step is the definition of the dispatching rules that will redirect the objects to an appropriate classifier. Especially, the idea is to take advantage of dispatching for detecting whether a shape is a circle or a square. In this case, two rules are needed: one that evaluates to true the circle polygons and another one which evaluates to true square polygons. One way to distinguish circles and squares is using the circularity shape factor. It is a real value between 0 and 1 which measures how close the shape of an object is to that of a circle. Especially, perfect circles have a circularity 1 and straight lines have a circularity 0. In this case, because the shape is discretized in the image, the algorithm will never produce perfect circles so detecting circular shapes must be done by thresholding the circularity. Particularly, polygons having a circularity greater than 0.85 can be considered circles while the others can be considered squares. The implementation of the dispatching rules are given in Listing 3.2. Thanks to the Python list comprehension syntax, the definition of the rules is again really concise.

Now that the segmentation and dispatching rules are defined, the last missing element is the classifier. In this case, it should produce the last desired information which is the color of the shapes. A simple idea is to use the polygon to retrieve the central pixel of the shape. Then, the greyscale value of this pixel can be checked to identify whether the color of the shape is white or grey. The implementation of the classifier is given in Listing 3.3. In the context of this example, the image to be processed might not be large. However, the classifier is implemented so that the full image is never loaded into memory. Indeed, before extracting the pixels, the window boxing the polygon is extracted from the image and only the NumPy representation of this window is loaded into memory (see `image.window_from_polygon()` and `window.np_image` method calls).

Listing 3.1: Toy example - Encapsulating custom image format

```
class NumpyImage(Image):
    """An image represented as a NumPy ndarray"""
    def __init__(self, np_image):
        self._np_image = np_image

    @property
    def np_image(self):
        return self._np_image

    @property
```

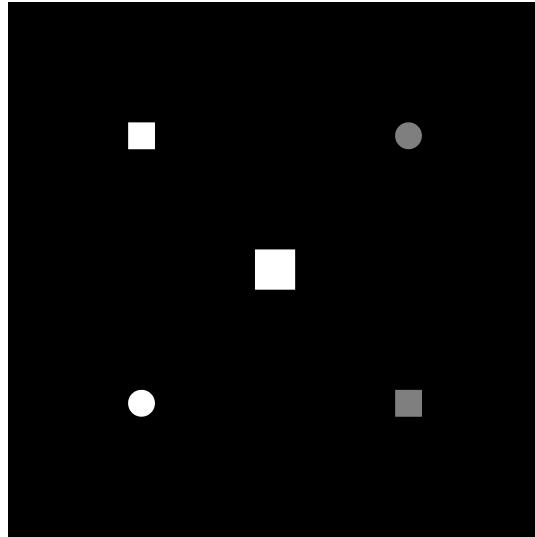


Figure 3.12: Example image to be processed for the toy example

```

def channels(self):
    shape = self._np_image.shape
    return shape[2] if len(shape) == 3 else 1

@property
def width(self):
    return self._np_image.shape[1]

@property
def height(self):
    return self._np_image.shape[0]

```

Listing 3.2: Toy example - Dispatching rules

```

class CircleRule(DispatchingRule):
    """Dispatching rule which matches circles"""
    def evaluate_batch(self, image, polygons):
        return [circularity(polygon) > 0.85 for polygon in polygons]

class SquareRule(DispatchingRule):
    """Dispatching rule which matches squares"""
    def evaluate_batch(self, image, polygons):
        return [circularity(polygon) <= 0.85 for polygon in polygons]

```

Listing 3.3: Toy example - Classifier

```

class ColorClassifier(PolygonClassifier):
    """Classifier that predicts the color of a shape"""
    GREY = 0
    WHITE = 1
    def predict_batch(self, image, polygons):
        classes = []
        for polygon in polygons:
            # Fetch center pixel
            window = image.window_from_polygon(polygon)
            sub_image = window.np_image
            c_x = int(polygon.centroid.x) - window.offset_x
            c_y = int(polygon.centroid.y) - window.offset_y
            pxi = sub_image[c_y][c_x]

```

```

# Generate the label based on the pixel color
if pxi == 255:
    classes.append(self.WHITE)
elif 0 < pxi < 255:
    classes.append(self.GREY)
else:
    classes.append(None)
return classes, [1.0] * len(polygons)

```

Listing 3.4: Toy example - Segmentation implementation

```

class CustomSegementer(Segmenter):
    """Every non black pixel are in an object of interests"""
    def segment(self, image):
        return (image > 0).astype("uint8")

```

Listing 3.5: Toy example - Applying the framework

```

# Build the workflow
builder = WorkflowBuilder(n_jobs=1)
builder.set_segementer(CustomSegementer())
builder.add_classifier(CircleRule(), ColorClassifier())
builder.add_classifier(SquareRule(), ColorClassifier())
workflow = builder.get()

# Execute
results = workflow.process(NumpyImage(image))

```

Chapter 4

SLDC at work : the thyroid case

In this chapter, the *SLDC* framework is applied the problem presented in Chapter 2 : the nodule malignancy assessment. This problem is effectively an instance of the objects detection and classification problem. Indeed, the goal is to diagnose malignancy by the presence or absence of cells or groups of cells having particular characteristics in digitized microscope whole-slide. This problem is a good use case for the *SLDC* framework: the images are large (i.e. typically 15 giga-pixels), two distinct categories of objects must be found (namely cells and groups of cells) and some of these objects can be included into others which can be handled using dispatching and chaining.

An introduction to the thyroid problem as well as the underlying implementation challenges are presented in Section 4.1. Then, the workflow developed in [Deb13] is briefly presented and its performances are assessed in Section 4.2. Especially, some flawed steps are highlighted and some improvements are proposed. Then, the implementation of the improved workflow is detailed in section 4.3. Finally, the performances of this implementation are analyzed in Section 4.4.

4.1 Problem and underlying challenges

The problem consists in finding cells with inclusions and proliferative architectural patterns in large digitized microscope slides. To perform this detection, a dataset containing approximately 5700 annotations was created by experts on the Cytomine platform. The major challenges involved with this problem are detailed hereafter.

Image quality While the images resolution is more than acceptable, the images themselves are by nature not very well suited for object extraction. Indeed, the objects of interests are surrounded with a lot of other undesirable objects. Moreover, due to the imprecise nature of the staining performed before digitization, some staining variations appears from one slide to another but also within a single slide.

Image size As explained in Section 2.2.1.2, the size of the images ranges from 4 giga-pixels to 18 giga-pixels. Therefore, the various processing steps should be as efficient as possible to avoid huge execution times. Also, accessing the images must be done through HTTP requests. Therefore, a particular attention should be paid to the number of requests to be executed for fetching the image. Especially, some caching policy might be needed to reduce the network time overhead.

Class imbalance The dataset of annotations is relatively balanced if all terms are considered separately. However, grouping terms for expressing the detection as a binary (or ternary) problem results in a major class imbalance, especially for the cells with inclusion versus normal cells problem.

Human annotations The human annotations are imperfect as experts usually annotate objects roughly (i.e. an annotation can be larger than the actual object). Moreover, some annotation drawing tools provided on the Cytomine platform generate particular shapes such as circles or rectangles. Assuming that an algorithm will annotate the cells more precisely, the resulting differences in terms of geometry and information content of the crops might lead to poor results if the experts annotations are used as learning data.

4.2 First workflow

The workflow developed by Antoine Deblire in [Deb13] is summarized in Figure 4.1. The idea behind this workflow is fairly simple. A first segmentation is applied to extract standalone cells and architectural patterns (step 4.3). The detected objects are then differentiated using their area and circularity (step 4.4) and dispatched to a classifier (steps 4.6). Especially, architectural patterns are classified as proliferative or non-proliferative by a first classifier and the cells are classified as inclusion or normal by a second one. Then, architectural patterns are segmented again (step 4.5) to extract the cells they contain and those cells are also passed to the cell classifier.

4.2.1 Segmentation procedures

The first segmentation procedure was designed for processing the whole slide and relies on a process called color deconvolution [RJ01]. This process consists in retrieving the tissues stains concentration from the RGB image. It appears that cells and patterns have a high concentration of a certain stain in the project images. Therefore, a first segmentation mask is generated by thresholding an image of which each pixel contains an integer value representing the stain concentration for the same pixel in the original image. Some morphological operations are then applied in order to remove noise and fill unwanted holes. Some example segmentations are provided in Figure 4.2. It seems that the procedure is able to detect most of the objects of interest although it sometimes fails at covering the whole object area. For instance in the third example image, there is a hole in the mask inside the pattern and this hole covers some cells that should be included in the mask. On the fourth example, one can see three standalone objects above the central pattern. Those objects' masks are smaller than their corresponding cells.

The second segmentation procedure is applied to the architectural patterns and was designed to isolate individual cells inside those patterns. The implementation is a little more complicated than the first. Similarly, it starts with a color deconvolution to highlight the cells. However, the stain concentration image is not transformed into a binary mask using a fixed threshold but using Otsu's method. Using the `findContour` procedure of the OpenCV library as well as morphological operations, independent cells are located and cleaned one after the other. Finally, a watershed algorithm is applied to separate cells that intersects. Some example segmentations are provided in Figure 4.2. The segmentation seems to work relatively well on "clean" patterns, that is where cells doesn't overlap much and are clearly distinguishable from the pattern background (see the first two examples in Figure 4.2). One "dirty" patterns however, the segmentation performs poorly as it either

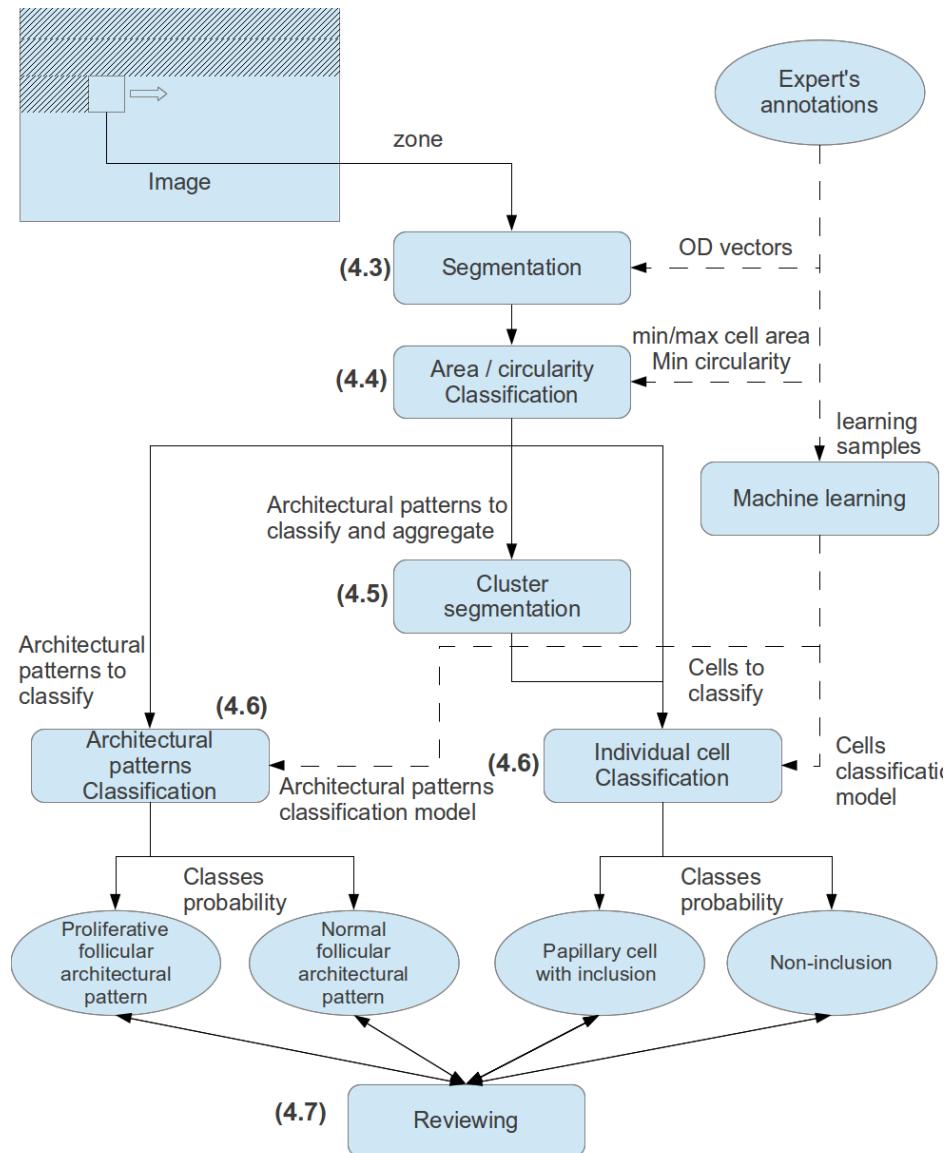


Figure 4.1: Antoine Deblire's workflow (source: [Deb13])

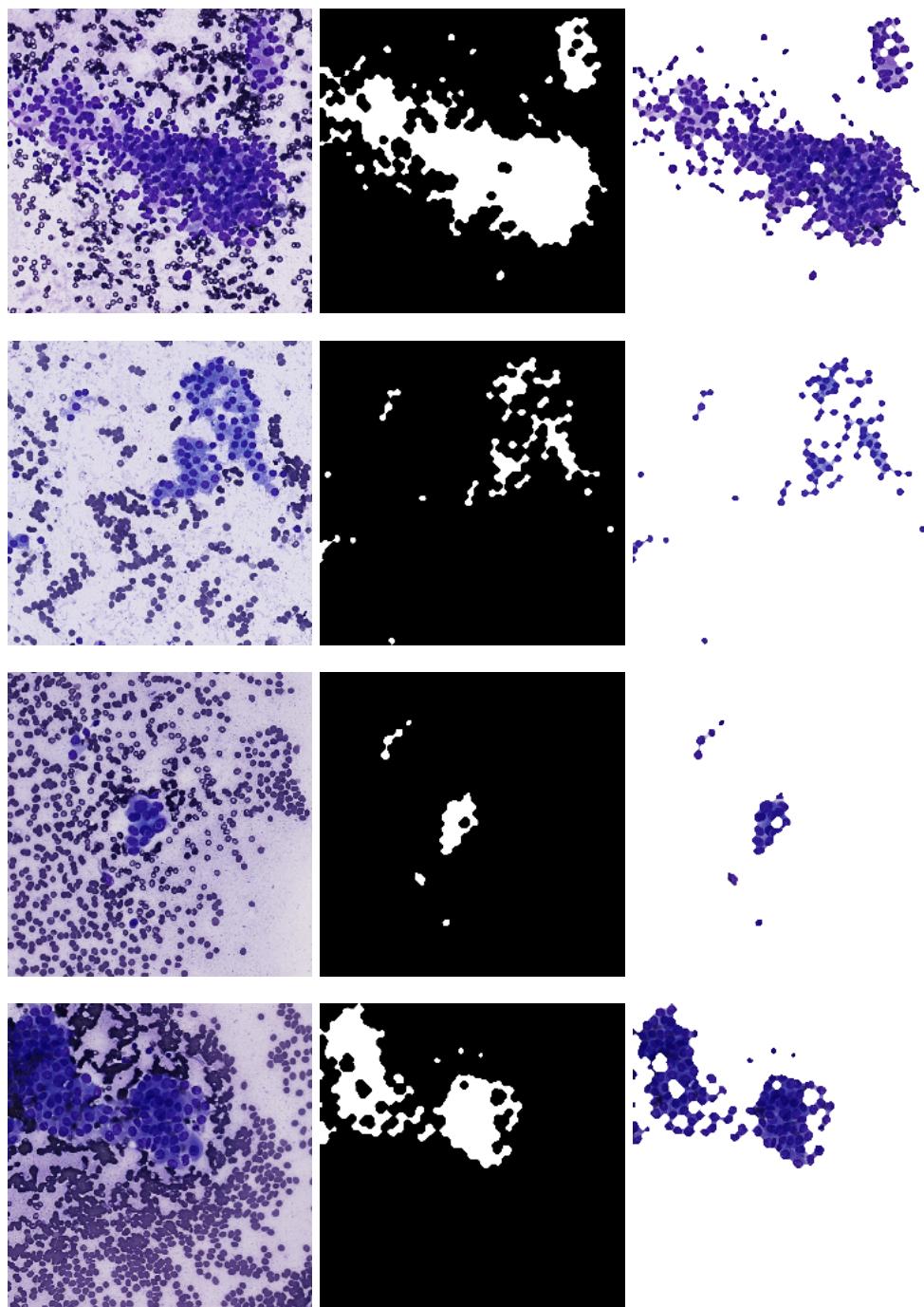


Figure 4.2: First segmentation - examples

A_{min}	$31 \mu m^2$
A_{max}	$102 \mu m^2$
C_{min}	0.7
N_{min}	4

Table 4.1: Dispatching parameters presented in [Deb13]

returns large patches which doesn't correspond to cells or fails to separate overlapping cells.

While the presented segmentation procedures exhibit some flaws, they were considered acceptable to test the *SLDC* framework.

4.2.2 Dispatching procedure

The step (4.4) consists in dispatching detected objects into four categories: artefacts, cells, clusters and patterns. The categories *artefact* and *cluster* respectively correspond to irrelevant objects and to groups of cells that contains too few of them to be patterns. Even if the author distinguishes patterns and clusters at the dispatching step, objects of both categories are treated equally in the subsequent steps of the algorithm. That is, they are first evaluated by the pattern classifier (for assessing whether they are proliferative or not) and they then are re-segmented. The dispatching is based on four parameters, the cell minimum and maximum areas (respectively, A_{min} and A_{max}), the cell minimum circularity C_{min} and the minimum number of cells per pattern N_{min} . The values of those parameters are given in Table 4.1.

Given A the area of the object of interest, the dispatching rules can be summarized as follows:

- **Artifact:** every object having an area less than A_{min} or and area less than A_{max} and a circularity less than C_{min}
- **Cell:** every object having an area such that $A_{min} < A < A_{max}$ and a circularity greater than C_{min}
- **Clusters:** every object of which the area is greater than A_{max} and such that it contains at most N_{min} cells:

$$A_{max} < A < N_{min} \times A_{max}$$

- **Patterns:** all objects which don't match one of the rule above are considered patterns

The author fixed the dispatching parameters values based on the areas and circularities of experts' annotations. As explained in Section 4.1, using those annotations to perform such a task might not be an good idea. Especially, the computed minimum and maximum areas might be a greater than the actual minimum and maximum areas of cells.

In order to assess whether the dispatching rules are effective for distinguishing cells from patterns, the expert annotations present on Cytomine were used. While those annotations shouldn't be used for setting the parameters, their usage for assessing the method is acceptable. Indeed, in this case, only a qualitative analysis is performed.

The histograms given in Figures 4.4 and 4.5 respectively show the area and circularity distributions of the experts' annotations. First, it appears that, whatever the metric,

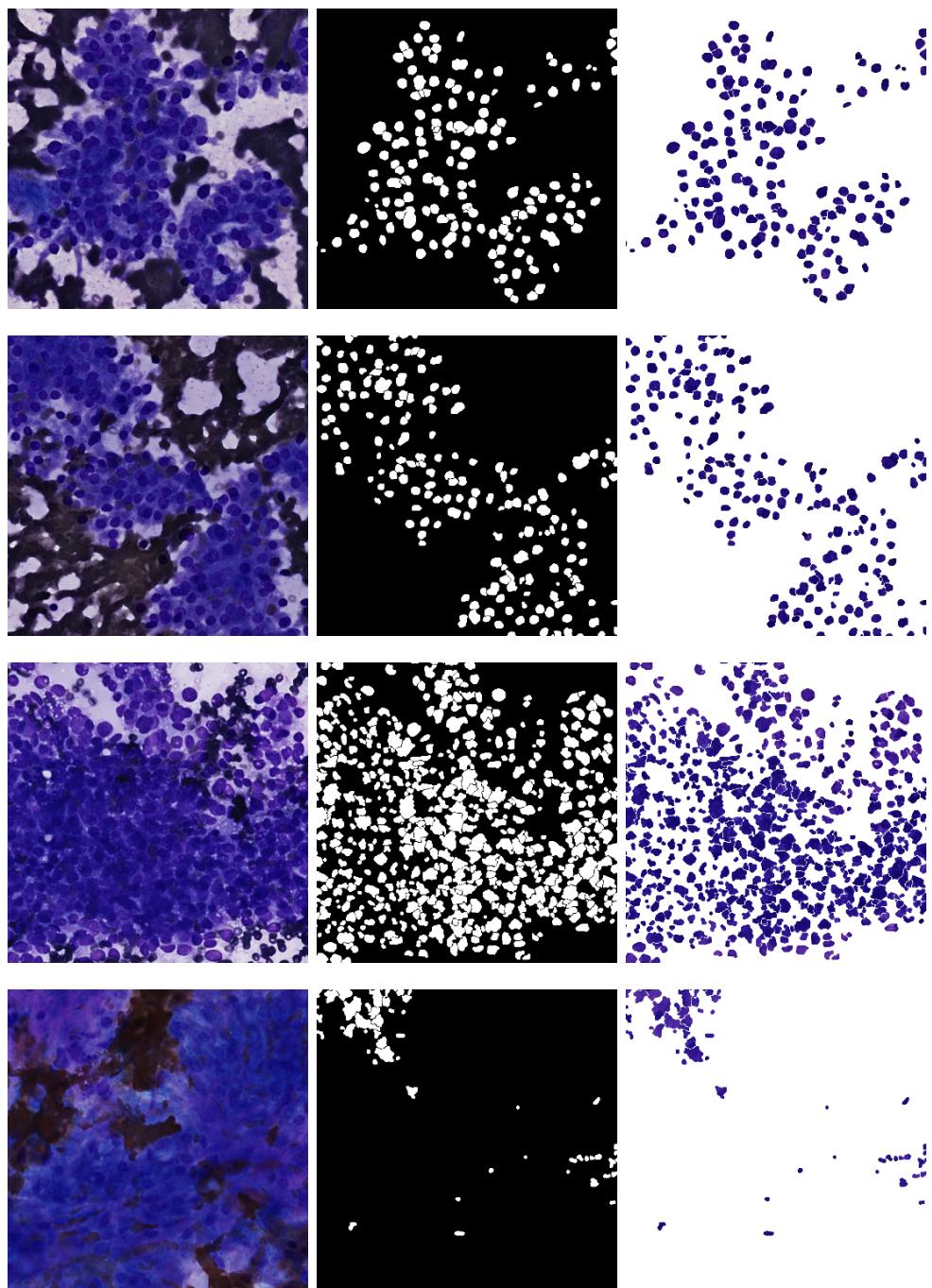


Figure 4.3: Second segmentation - examples

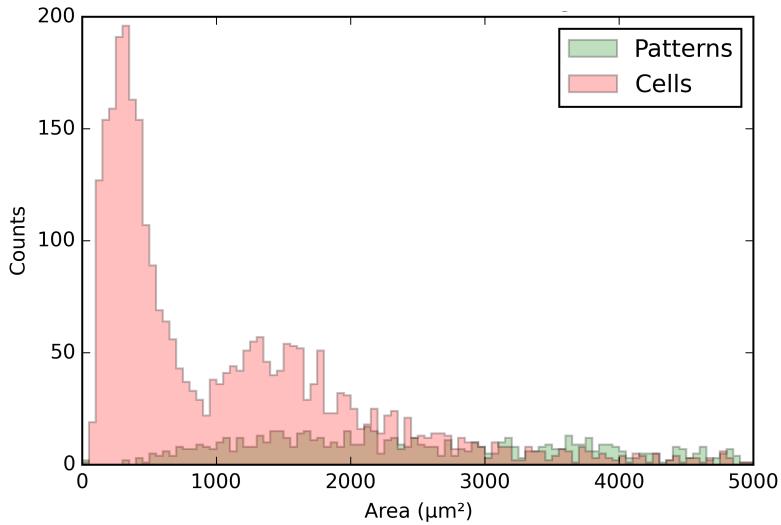


Figure 4.4: Area distributions of the experts' annotations.

there is a substantial overlapping between the cells' and patterns' distributions. This has a major consequence for the dispatching procedure presented above. Indeed, as it relies on simple thresholdings, it is ineffective at separating the objects because of the overlapping. Another observation is that the parameters given in Table 4.1 are not relevant as most of the cells would be dispatched as patterns with such values. This observation is confirmed with the scatter plot shown in Figure 4.6. In this plot, only few cells are effectively dispatched as such (see the blue box in the top left corner of the plot), the others being dispatched as patterns. Given those observations, it is clear that the dispatching procedure must be re-worked.

4.2.2.1 Improvement

As relying solely on geometrical properties is not a viable solution, an alternative consists in using the objects' crop image. Especially, the objects' crop would be classified into one of the dispatching categories (i.e. cell, pattern or other) using the random subwindows image classification algorithm [MGW16] (this algorithm is detailed in Appendix C). A drawback of this solution is that the dimensions of the objects are completely ignored. Given that some patterns might have a similar appearance than cells (color and shape), this might lead to misclassification.

To overcome the possible problems with the first solution, one could include the geometrical information of the polygons into the learning and prediction processes of the random subwindows algorithm. Especially, the circularity and area would be appended to the feature vector used by the SVM classifier to perform the image classification. This simple operation might not be sufficient however. Indeed, as the features extracted from the ensemble of randomized trees are numerous, the two geometric features would probably not contribute much to the prediction. To overcome this issue, a kernel could be used to increase the contribution of the geometric features. Whereas this solution might yield better results than the first, it requires the experts' annotations of the learning set to be cleaned to avoid the problem mentioned in Section 4.1. Moreover, it would require a non-negligible modification of the random subwindows algorithm. It was therefore considered

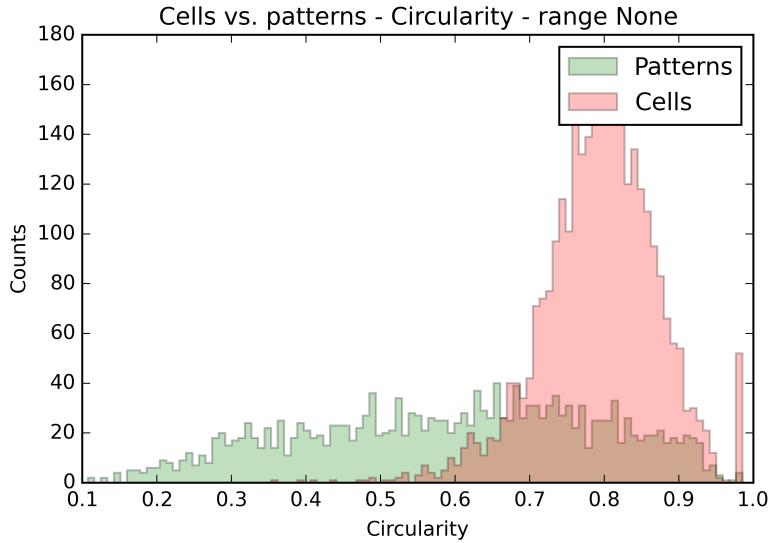


Figure 4.5: Circularity distribution of the experts' annotations.

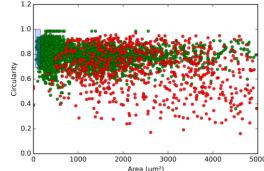


Figure 4.6: Scatter plot, circularity versus area. Green and red dots correspond respectively to cells and patterns. The blue box is the cell dispatching zone.

out of the scope of this thesis and the first proposed solution was retained.

4.2.3 Classification

As soon as objects are dispatched, they have to be classified. In [Deb13], the author uses two classification models: one for cells and another one for patterns. For patterns, a ternary classifier is used and predicts three classes: *proliferative pattern*, *non-proliferative pattern* and *others*. The author states that the third class is needed because with a binary classifier, some objects were classified as patterns while they were not. Hopefully, with the new dispatching procedure, those objects will be eliminated before reaching the classifier. It was therefore decided to use a binary classifier for performing this classification.

As far as the cell classifier is concerned, it predicts two classes: *cells with inclusion* and *non-inclusion*. In addition to the term *cell with inclusion*, the author includes the pseudo inclusions in the positive class.

The performance study for the various classifiers is given in Section 4.4.1.

4.3 Implementation

Following the *SLDC* framework philosophy, the problem dependent components have to be defined: an image representation, the segmentation procedures, the dispatching rules and the classifiers. Whenever possible, the components were developed to be reusable

for other applications within Cytomine. Those generic components are colored in blue in UML diagrams while the components dependent on the thyroid problem are colored in green.

4.3.1 Image representation

The first component to be defined is the actual representation of the images to be processed, that is, the digitized microscope slides stored on the Cytomine platform. This representation is implemented in the `CytomineSlide` class which stores an `ImageInstance`¹ object containing all the information about the slide including its width, height and identifier. To prevent anyone from loading the full image into memory, the implementation of the `np_image` raises the `NotImplementedError` exception.

In general, when the full image can be loaded into memory the default `Tile` class can be used. In this case, as this operation is impossible, a class `CytomineTile` was created to handle the tile image loading. Especially, the call to `np_image` triggers an HTTP requests to the Cytomine server to fetch the corresponding image window. If the request fails (e.g. HTTP error) or returns an invalid result (e.g. returned image has an invalid size), a `TileExtractionError` is raised as advised in the documentation. The class `CytomineTileBuilder` was created to build `CytomineTile` objects.

In order to reduce the overall execution time of the workflow, it is essential not to execute two times a same HTTP request for loading the image of a tile. To avoid this, the class `TileCache` was developed. It implements a simple caching policy using the local file system: when an image window is needed, the `TileCache` object first checks whether this image was already downloaded. If that is the case, the image can be loaded from the disk. Otherwise, the image is fetched by calling the `np_image` method of the underlying tile and stored on the disk before being handed back to the caller. The class also provides methods for adding an alpha mask to the returned image.

Some additional classes were developed to handle the addition of an alpha mask to an image window (class `CytomineMaskedWindow`) and to a tile (classes `CytomineMaskedTile` and `CytomineMaskedTileBuilder`). This feature is needed for the pattern segmentation procedure which assumes that an alpha mask indicating the position of the pattern is passed with the numpy array. To avoid storing an image representing the alpha mask into the classes, the mask is represented by a polygon.

The UML diagram of the package containing the image related classes is shown in Figure 4.7.

4.3.2 Classifier

All the classification tasks to perform in the context the thyroid problem are performed using the random subwindows algorithm [MGW16]. Especially, a Python implementation called Pyxit taken from Cytomine [Mar+16] was used. The central class of this implementation is the `PyxitClassifier` class which provides an scikit-learn-like interface to the algorithm (i.e. the methods `fit`, `transform`, `predict`,...). In order to use this class within the framework, a class `PyxitClassifierAdapter` was developed. The `predict_batch` method is implemented as follows.

First, the crops of the polygons passed to the method are fetched and stored on the disk using a `TileCache` (thanks to the cache, the HTTP request is only executed the first time the crops are requested). Because there can be a lot of polygons, the fetching of the crops is parallelized and the number of available processes can be specified at the

¹The `ImageInstance` class is defined in the Cytomine Python client

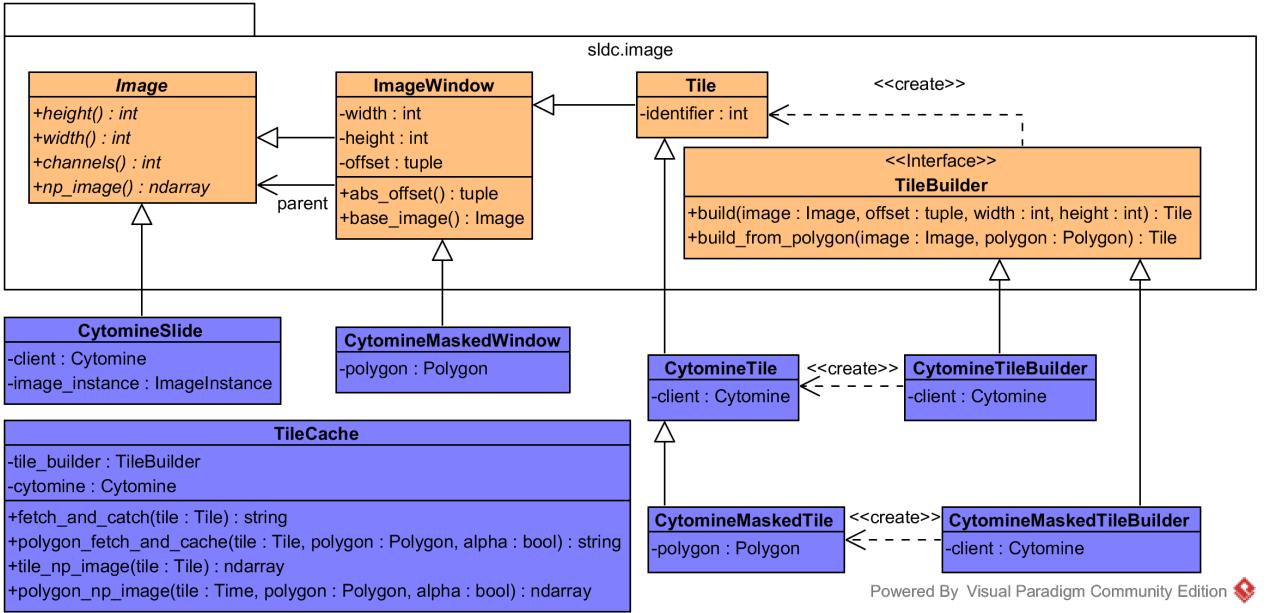


Figure 4.7: UML diagram - Cytomine image representation

construction of the `PyxitClassifierAdapter` object. Each available process is passed a set of polygons of which the crops must be fetched in order to reduce the serialization overhead (see Section 3.2.4.10). If some crops cannot be fetched whatever the reason, the corresponding polygons are associated a class `None` and a probability 0. Moreover the user is notified with the logger about the crops that couldn't be fetched.

As Pyxit works with images stored on the disk, a list containing the filepath of the images to classify is generated and passed to the `_predict` method. This method implements the generation of the classification labels and probabilities. If a SVM classifier was provided at construction of the `PyxitClassifierAdapter` object, then the variant of the random subwindows algorithm that uses the extremely randomized trees as feature learner is used. That is, the Pyxit classifier is used to generate the features that are passed to the SVM classifier for predicting the labels. Otherwise, the variant that uses the extremely randomized trees as direct classifier is used.

Finally, the `predict_batch` method aggregates the results returned by the `_predict` method with the fake labels and probabilities generated for the polygons of which the crops couldn't be fetched.

A static method is also provided for constructing a `PyxitClassifierAdapter` object from a serialized Pyxit model. Especially, the method deserializes the `PyxitClassifier` object as well as the SVM classifier if one is provided and passes them to the adapter's constructor. This method also sets the number of processes to use for fetching the crops. If the number of available processors is less than five, then all of them are used to fetch the crops. Otherwise, five processors are used. This value was chosen in order to avoid overloading Cytomine server when the number of available processors is high.

The UML diagram of the `PyxitClassifierAdapter` class is shown in Figure 4.8.

4.3.3 Dispatching rules

As explained in Section 4.2.2, the chosen dispatching method relies on a classifier of which the predicted class is the dispatching index. Especially, the classifier was built to predict

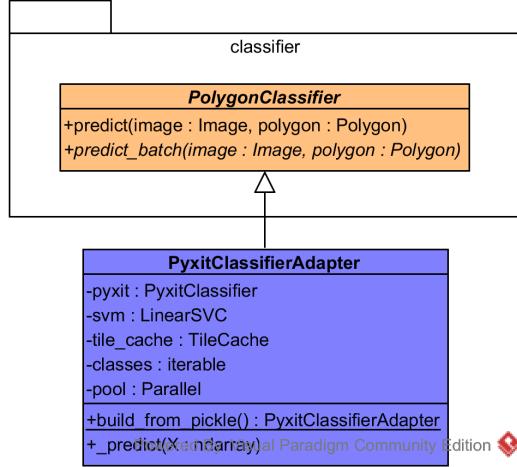


Figure 4.8: UML diagram - Classifier

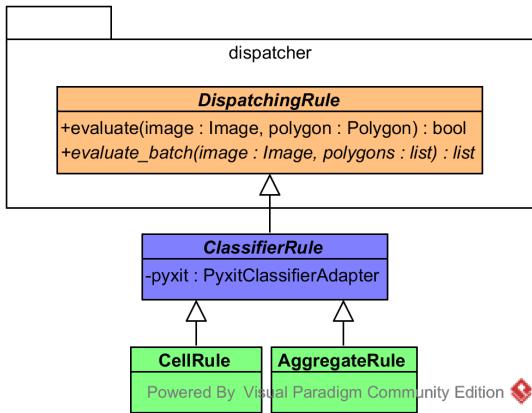


Figure 4.9: UML diagram - Thyroid workflow dispatching rules

the label 0 for cells, 1 for patterns and 2 for the other objects.

To take advantage of the features provided by the class `PyxitClassifierAdapter` (i.e. caching, parallel fetching,...), it was reused and encapsulated in two classes extending `DispatchingRule`. The implementation of the rules' `evaluate_batch` method is therefore straightforward. It first calls the `predict_batch` method of the classifier adapter object and then generates a list of boolean values according to the returned classification labels. For the first rule, `CellRule`, `True` is associated to polygons of which the returned label is 0. For the second, `AggregateRule`, `True` is associated with polygons of which the predicted label is 1.

Unfortunately, this organization implies that the polygons marking patterns and other objects will be classified two times by the same classifier. Indeed, because of the dispatching structure imposed by the framework, the polygons that are not matched by the first rule are evaluated by the second. This could be avoided by refactoring the framework or by implementing another dispatching strategy.

The UML diagram containing the dispatching rule classes is shown in Figure 4.9.

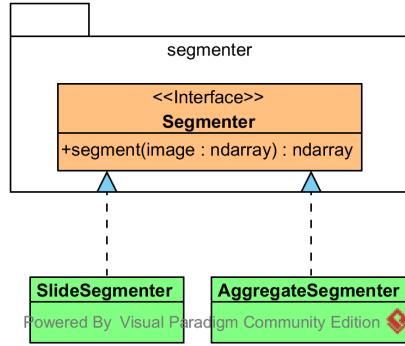


Figure 4.10: UML diagram - Segmenter classes

4.3.4 Segmentation

The segmentation procedures were implemented in two classes, `SlideSegmenter` and `AggregateSegmenter`. Both implementation were taken from Antoine Deblire's source code. Whereas the slide segmentation could be used almost directly without modification, the recovered aggregate segmentation procedure didn't work. It was therefore re-implemented following the explanations provided in the master thesis as well as the few comments present in the source code. After few tests, it appeared that both segmentation procedures were really slow because of the color deconvolution. Especially, to execute the color deconvolution on a 4 mega-pixels image yielded more than 2 seconds execution time. A first optimization pass was done over the function in order to reduce its execution time to 1 second (same image dimensions). The UML diagram containing the segmenter classes is shown in Figure 4.10.

4.3.5 Chaining

The chaining package of the framework must be used to define which detected objects (i.e. the patterns) must be re-segmented. First, an image provider must be defined to generate the `CytomineSlide` to be processed. This logic is implemented in the `SlideProvider` class. Then, the selection of the objects to be processed by the second workflow must be defined as a `WorkflowExecutor`. Especially, the class `AggregateWorkflowExecutor` was implemented to fulfill this role. The class defines the method `get_windows` which implements the selection of objects to be re-segmented and the generation of `CytomineMaskedWindow` objects to be processed by the second workflow. Moreover, it extends the class `PolygonTranslatorWorkflowExecutor` because the polygons generated by this phase needs to be translated back into the full image reference system. The final component to be defined is the post processor which is passed all the detected objects and their classes. In the context of the thyroid problem, the post processor should upload the generated polygons and classes as annotations on the Cytomine platform. This logic is implemented in the `post_process` method of the `ThyroidPostProcessor` class. Unfortunately, the Cytomine API doesn't provide any request for uploading annotations by batches and each annotation has to be added with two HTTP requests: one for uploading the geometry and another for uploading the predicted class and associated probability. To avoid waiting for each request to terminates before sending another one, the process was parallelized. The UML diagram containing the chaining classes is shown in Figure 4.11.

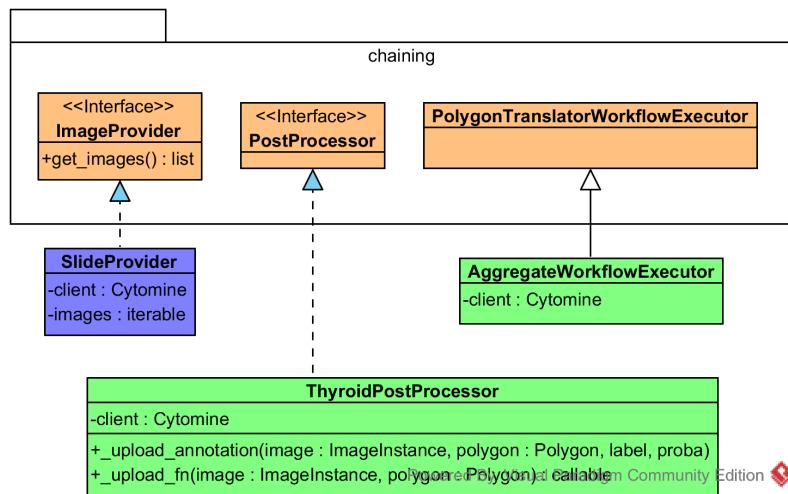


Figure 4.11: UML diagram - Chaining classes

4.4 Performance analysis

4.4.1 Classification models

4.4.1.1 Test set and cross validation

4.4.1.2 Dispatching model

4.4.1.3 Pattern classifier

4.4.1.4 Cell classifier

4.4.2 Execution times

4.4.3 Memory

4.4.4 Overall

Chapter 5

Conclusion

Appendix A

Tile topology

As presented in Section 3.2.4.1, the tile topology objects associate unique increasing identifiers to tiles. Using this representation allows to reach a $\mathcal{O}(1)$ time complexity for all the methods of the class `TileTopology`. Indeed, the results produced by those methods can be computed using simple formulas. In the following formulas, i refers to a tile identifier:

- The number t_{row} of tiles on a row is given by:

$$t_{row} = \begin{cases} \left\lceil \frac{w - o_p}{w_m - o_p} \right\rceil & , \text{ if } w > w_m \\ 1 & , \text{ otherwise} \end{cases} \quad (\text{A.1})$$

- The number t_{col} of tiles on a column is given by Equation A.1 applied to the image height h and maximum tile height h_m instead of w and w_m .
- The total number t of tiles in the tile topology is simply $t_{row} \times t_{col}$.
- The neighbour tiles identifiers can be obtained by performing subtractions and additions. For instance, for a tile which is not on the edge of the image, the identifiers of its left, top, right and bottom neighbours are respectively $i - 1$, $i - t_{row}$, $i + 1$, $i + t_{row}$.
- The tile offset $(t_{off,x}, t_{off,y})$ can be retrieved as follows:

$$t_{off,x} = (t_{row} - o_p) \times [(i - 1) \mod t_{row}] \quad (\text{A.2})$$

$$t_{off,y} = (t_{col} - o_p) \times \left\lfloor \frac{i - 1}{t_{row}} \right\rfloor \quad (\text{A.3})$$

Appendix B

Ontology

The ontology associated with the Thyroid project on Cytomine is the following:

1. Architectural patterns:

- Normal follicular architectural pattern
- Proliferative follicular architectural pattern
- Proliferative follicular architectural pattern (minor sign)

2. Nuclear features:

- Papillary cell NOS
- Normal follicular cells
- Normal follicular cell with pseudo-inclusion (artefact)
- Papillary cell with ground glass nuclei
- Papillary cell with nuclear grooves
- Papillary cell with inclusion

3. Others:

- Macrophages
- Red blood cells
- PN (polynuclear)
- Colloid
- Artefacts
- Background

Appendix C

Random subwindows

Random subwindows [MGW16] is an image classification algorithm. The first step of the algorithm consists in transforming the N input images. This is done by extracting a set of N_w random subwindows from each image. A random subwindow is a square patch of random size extracted at a random position in an image. The extracted windows are then resized to a fixed size patch (w, h) . Those transformation operations generates a dataset containing $N \times N_w$ objects and $w \times h$ attributes.

The second step consists in passing this dataset to a classifier which will actually predict the image's classification label from those subwindows. In [MGW16], two classification methods are proposed.

The first uses extremely randomized trees [GEW06] as direct classifier: that is, each window is predicted a label and the full image label is determined by a majority vote over the predicted classes of this image's windows.

The second variant uses extremely randomized trees as feature learner rather than a direct classifier and relies on a SVM classifier to produce the prediction. In this variant each image is represented as a vector of which the dimensionality equals the number of terminal nodes in the ensemble of randomized trees and where the i^{th} feature is the number of windows that reached the i^{th} leaf node of the forest divided by the total number of windows. This vector is then passed to the SVM classifier to predict the image classification label.

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