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Towards semantic-driven high-content image analysis: An operational instantiation for mitosis detection in digital histopathology

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ABSTRACT

This study concerns a novel symbolic cognitive vision framework emerged from the Cognitive Microscopy (MICO[1]) initiative. MICO aims at supporting the evolution towards digital pathology, by studying cognitive clinical-compliant protocols involving routine virtual microscopy. We instantiate this paradigm in the case of mitotic count as a component of breast cancer grading in histopathology. The key concept of our approach is the role of the semantics as driver of the whole slide image analysis protocol. All the decisions being taken into a semantic and formal world, MICO represents a knowledge-driven platform for digital histopathology. Therefore, the core of this initiative is the knowledge representation and the reasoning. Pathologists' knowledge and strategies are used to efficiently guide image analysis algorithms. In this sense, hard-coded knowledge, semantic and usability gaps are to be reduced by a leading, active role of reasoning and of semantic approaches. Integrating ontologies and reasoning in confluence with modular imaging algorithms, allows the emergence of new clinical-compliant protocols for digital pathology. This represents a promising way to solve decision reproducibility and traceability issues in digital histopathology, while increasing the flexibility of the platform and pathologists' acceptance, the one always having the legal responsibility in the diagnosis process. The proposed protocols open the way to increasingly reliable cancer assessment (i.e. multiple slides per sample analysis), quantifiable and traceable second opinion for cancer grading, and modern capabilities for cancer research support in histopathology (i.e. content and context-based indexing and retrieval). Last, but not least, the generic approach introduced here is applicable for number of additional challenges, related to molecular imaging and, in general, to high-content image exploration.

1. Introduction

Cancer is a deadly disease and major cause of death worldwide. Every year, 7.4 million people (about 13% of the people dying worldwide [1]) die because of cancer.

Breast cancer is a very common type of cancer, especially for woman, for whom it comprises 22.9% of all cancers [2]. Breast cancer is also a very deadly disease. In 2013, 234,580 new cases and 40,030 deaths from breast cancer are estimated in the United States [1]. The estimated new cases of breast cancer in the United States in 2013 were about 232,340 cases in female and 2240 in male. The mortality was about 39,620 cases for female and 410 for male, with 1 woman out of 57 sick dying from breast cancer [1]. About 1 in 8 US women (almost 12%) developed invasive breast cancer over the course of her lifetime [1].[2] In Europe, breast cancer is the most current form of cancer for women, with 42,000 new cases a year [3].

The last few decades, digital technologies have been emerging on the market, like high resolution histopathological slide scanners or efficient software viewers for large-scale histopathological

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[1] MICO – a French National Research Agency, Technologies for health and autonomy (ANR TecSan) project: https://www.comp.nus.edu.sg/~danielr/projects.htm.

[2] http://www.breastcancer.org.

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images. Similarly, pattern recognition image processing algorithms have been shown to be quite effective and mature for medical applications [4]. However, these technologies are still not being intensively used in pathology departments, and will not be adopted without being properly adapted to the medical domain and practices.

Cautious in creating and respecting new protocols in digital pathology, this study proposes a novel approach in cognitive vision, combining imaging, reasoning and ontologies. The work has been done in the framework of the Cognitive Microscopy project (MICO[1]), dealing with a cognition-driven visual explorer for breast cancer grading. The traceability of a second opinion being a key issue, the proposed system is so able to explicitly consider the visual (and contextual) medical knowledge, by indicating at each step, the rules and the ontologies used to generate the quantitative diagnosis support.

After presenting the challenge of the cognitive virtual microscopy, we analyse the problem of knowledge representation in digital histopathology, in order to further describe the effective use of reasoning, ontologies and imaging tools, in the context of breast cancer grading.

2. Cognitive virtual microscopy

Histopathology became widely accepted as a powerful exam for diagnosis and prognosis in mainstream diseases such as breast cancer. Currently, analysis of medical images in histopathology largely remains the work of human experts. For the pathologists, this consists in hundreds of slides examined daily,[3] a tedious repetitive work which will greatly benefit from reliable and traceable digital second opinion. Beside, the work of a pathologist is mostly based on an intensive visual micro-semiology training (at least a decade to reach a real expertise in most of specialties) and know-how, embedded in a very complex medical contextual knowledge.

In this sense, considering the cognitive part of the pathologist's work is essential when we envisage a reliable second opinion support. The Cognitive Microscope (MICO[1]) initiative aims at developing a cognition-driven visual explorer for histopathology, focusing on the use case of mitotic count in breast cancer grading. MICO proposes a radical change in medical practice by proposing a cognition-driven medical imaging environment, enabling safer decision support in histopathology.

The system integrates image visualisation and exploration support, as the use of specific visual medical knowledge, in order to set up the bases of a cognition-driven medical imaging, able to address pervasive adaptation and physical-virtual confluence challenges for histopathology. The analysis capabilities and results are made available to the pathologist through a platform combining virtual microscopy and cognitive reasoning. This allows medical staff to interact with the platform at the appropriate level of abstraction. The platform combines multi-scale whole slide image (WSI) exploration and analysis, as medical knowledge representation and inference using ontologies.

Among the existing cognitive vision approaches [5], we chose to go for the symbolic one, enabling a better interaction with the users (the pathologists – in our case), a traceability for verification and quality control, as an effective maintenance capability, by using referenced on-line medical thesauri (Snomed-CT,[4] ADICAP[5] etc.).

[3] For example, at the Pitié-Salpêtrière Hospital, Paris, about 1500 slides need to be examined daily by the Pathology Department.

[4] SNOMED Clinical Terms (Snomed-CT): ihtsdo.org/snomed-ct.

[5] French Association for the Development of the Informatics in Cytology and Anatomo-Patholog (ADICAP): adicap.asso.fr.

3. Knowledge representation in histopathology

Histopathology is the study of signs of disease using the microscopic examination of a biopsy or surgical specimen processed and fixed onto glass slide [6]. Histopathologists often are experts able to analyse tissue samples on glass slide using light microscope to grade cancers [3]. Sample observation is important because it allows the expert to make a judgement on the state of the disease. Therefore, it helps to target the appropriate cure. Histology involves invasive procedures and is the most accurate way of grading cancers so far. The histopathological diagnosis plays also a legal role in most of advanced countries.

Accurate grading of invasive breast cancer requires good fixation, processing, section cutting, staining and careful application of grading criteria.[6]

A pathologist may have to analyse different kind of biological, cytological or histological extractions. Since the cytology is the analysis of cells and no information is kept about their spatial organisation, the histology represents the study of a tissue. There are different techniques for tissue extraction. In the case of breast cancer, biopsy, tumorectomy, mastectomy or axillary curage may be operated, depending mostly on the nodule size. After its extraction, the tissue is analysed using a microscope. Fig. 1 shows an example of lesion induced by breast cancer [7].

3.1. Breast cancer grading

In case of solid tumour, cancer diagnosis is morphological and made using human tissue samples [3]. Histological slides (Fig. reffig:slide) are extracted from these samples. Histopathologists expertise enables medical diagnosis by the observation of these histopathological slides. Fig. 1 shows an example of what histopathologists may see using light microscope.

Histological grading helps to categorise the breast cancer, and therefore to treat it better. Breast cancer grading is now based on international standards. For a long period of time, the most widespread grading system has been the Scarff–Bloom–Richardson (SBR) system. Recently, the Nottingham Grading System (NGS) [8], a more reproducible variation of it [7], has become increasingly popular. Since 2003, NGS is the grading system recommended by the World Health Organisation.

The NGS consists in the study on three criteria, by establishing a cancer state evaluation protocol using of the respective scores. The three analysed criteria are tubules formation, nuclear pleomorphism and mitotic count [9]. A grade of 1 depicts a low level of cancer for the patient, while a grade of 3 means an advanced state of cancer. In the UK, in 2005, for example, about 20% of symptomatic breast cancers were grade 1, 30% grade 2, and 50% grade 3.[6]

Histopathological slide analysis is a complex task requiring advanced expertise. There are some drawbacks to the current histological grading process. Some grading tasks like counting mitosis can be very tedious and time consuming, inducing delay before diagnosis. Moreover, in most of the hospitals there are fewer and fewer experts, since increasingly important quantities of histopathological slides are produced every day.[3] Furthermore, one must admit that the criteria ruling histopathological analysis or grading are not fully formally described. Actually, there is currently no way to formally double-check judgements from histopathology experts about biological objects (for instance, it is very difficult to formalise how looks a mitosis and why a particular pattern corresponds to a mitosis). This lack of formalisation

[6] http://www.cancerscreening.nhs.uk.