Digital Pathology in Europe: Coordinating Patient Care and Research Efforts

Marcial GARCIA ROJO^{a,1}, Vytenis PUNYS^b, Janina SLODKOWSKA^c, Thomas SCHRADER^d, Christel DANIEL^e, Bernd BLOBEL^f

^a Hospital General de Ciudad Real, Spain

^b Kaunas University of Technology, Lithuania

^c Military Institute of the Health Services, Warsaw, Poland

^d University of Applied Sciences, Brandenburg, Germany

^e INSERM, Université René Descartes, Paris, France

^feHealth Competence Center, University Hospital Regensburg, Germany

Abstract. The COST Action IC0604 "Telepathology Network in Europe" (EURO-TELEPATH) is an initiative of the COST (European Cooperation in the field of Scientific and Technical Research) framework, supported by the Seventh Framework Programme for research and technological development (FP7), of the European Union will be running from 2007 to 2011 and is aimed to coordinate research efforts to develop the most adequate technological framework for the management of multimedia electronic healthcare records (data and images) applied to Anatomic Pathology. Sixteen countries are participating in EURO-TELEPATH. Activities are organized in four Working Groups (WGs): WG1 – Pathology Business Modeling, WG2 - Informatics Standards in Pathology, WG3 - Images: Analysis, Processing, Retrieval and Management, and WG4 - Technology and Automation in Pathology. During the first year of work, the collaboration between software engineers, computer scientists, pathologists and other clinicians has been essential to detect three main areas of interest in digital pathology research: virtual microscopy scanning solutions, health informatics standards, and image processing and analysis. Research in these areas is essential to a correct approach to telepathology, including primary diagnosis, and secondary or teleconsultation services. Managing microscopic pathology images (virtual slides) is a challenge to existing information systems, mainly due to its large size, large number, and complex interpretation. Regarding interoperability, the integration of pathology reports and images into eHealth records is an essential objective that research groups should consider. Promoting participation in standards bodies (DICOM, IHE, HL7, IHTSDO) is an essential part of the project work. Understanding the business process of pathology departments in daily practice, including healthcare, education, research, and quality control activities, is the starting point to be sure that standardization efforts converge with user needs. Following a recent IHE proposal, coordination with public health services like national or regional tumor registries must also be supported. Virtual or digital slides are fostering the use of image processing and analysis in pathology not only for research purposes, but also in daily practice. Nowadays, further discussion is needed on the adequacy of current existing technical solutions, including for instance quality of images obtained by scanners, or the efficiency of image analysis applications.

Keywords. digital pathology, telemedicine, medical informatics standards, interoperability IHE, DICOM, pathology business modeling, virtual slide, image analysis

Corresponding Author: Marcial García Rojo, Hospital General de Ciudad Real, Calle Tomelloso s/n. 13005 Ciudad Real, Spain; E-mail: marcial@cim.es; http://www.conganat.org/eurotelepath/.

1. Introduction

The COST Action IC0604 "Telepathology Network in Europe" (EURO-TELEPATH) is an initiative of the COST (European Cooperation in the field of Scientific and Technical Research) framework supported by the newest European Commission Research Framework Programme (FP7).

EURO-TELEPATH is aimed to coordinate research efforts to develop the most adequate technological framework for the management of multimedia electronic healthcare records (data and images) applied to Anatomic Pathology.

Based on common standards developed by European Normalization Committee (CEN), the World Wide Web Consortium (W3C) and other bodies like Digital Imaging and Communication in Medicine (DICOM), Health-Level Seven (HL7), and Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT), the direct result of this Action shall be collaboration with the Integrating the Healthcare Enterprise (IHE) initiative in the development of Anatomic Pathology Technical Framework (IHE Anatomic Pathology). This should be taken as a new reference standard by the specialized E-health industry as well as the entire medical community.

Sixteen countries are participating in EURO-TELEPATH. Activities are organized in four Working Groups: WG1 – Pathology Business Modelling, WG2 – Informatics Standards in Pathology, WG3 – Images: Analysis, Processing, Retrieval and Management, and WG4 – Technology and Automation in Pathology.

Three main topics of discussion are proposed:

- Research in general business process in pathology to help in the best use of existing standards (DICOM, HL7, jpeg, web services, reference terminologies, etc) to implement the business processes for both patient care and research in Anatomic Pathology. These standardization efforts conducted within IHE (Integrating the Healthcare Enterprises) [1] influenced the work of DICOM, HL7 and the JPEG community. The current IHE Anatomical Pathology Technical Framework ready for implementation and new Integration Profiles are defined every year [2].
- Images Analysis and Processing in Pathology has become an essential element of the modern diagnostic pathology. During this session physicians, biologists, and IT specialists can learn about emerging standards and the tools of digital pathology improving immunohistochemical evaluation of digital slides. It will be an opportunity to enter into a dialogue with the international experts involved in new trends of digital pathology.
- Automation in Digital Pathology research is aimed to analyze the integration of new automated instruments in pathology, including immunohistochemistry solutions. New research in microscopic digital imaging (virtual slide solutions, slide scanners) needs to be considered.

2. Pathology Business Modeling and Medical Informatics Standards

2.1. Business Processes in Pathology

In COST Action IC0604 we have developed a general business process in pathology to analyze and specify the requirements of integration of telepathology in routine diagnostic process, education, research, and quality control activities [3, 4]. The business process is designed as a best practice model and can be used for discussion and description of specific processes in a department [5].

The current model of business processes in pathology design in COST Action IC0604 will be presented, discussed and modified according to the requests and inputs from the participants. The flexibility and usefulness of business process modeling will be shown and explained in detail.

2.2. Informatics Standards in Pathology

In relation to the business models the current integration profiles addressed within IHE Anatomic Pathology Technical framework will be explained. "Integration profiles" are real-world situations describing exchange of information called *transactions* from various functional components of a distributed health care environment called *actors*. Integrating the Healthcare Enterprise, which has developed in North America, Europe, and Asia, provides implementation guides for transactions by using established industry standards such as DICOM or HL7. The annual definition cycle of new profiles by users and suppliers – ending in the organization of international platforms of interoperability tests (called "connectathons") – confers its unique efficiency, transforming basic standards into "plug and play" solutions. Prior integration profiles developed for radiologic imaging have been very successful. We will also address the issue of the participation of the Anatomic Pathology community in other standardization organizations such as IHTSDO, OBO Foundry or the JPEG community in order to take advantage of the most advanced results of these groups (reference biomedical ontologies, compression algorithms, etc).

2.3. A Data Model for Handling Whole Slide Microscopy Images in Picture Archiving and Communication System

Extremely large medical images, like virtual slide microscopy ones, are going beyond some limitations (e.g., a 4Gbyte barrier, caused by 32-bit architecture) of the DICOM (Digital Image Communication in Medicine) standard. Some solutions and trade-offs have been already proposed and included in the DICOM standard (e.g., usage of JPEG2000 image compression standard, JPEG2000 interactive protocol (JPIP) and division of images into smaller parts is being discussed, stored then in the PACS), though they might lead to implementation of some alternative interaction solutions simultaneously in the same PACS serving both images of typical size (e.g., radiological) and large size virtual slide microscopy images. The following issues are being discussed: A problem of constructing a data and interaction model of images within PACS, looking for criteria to assess image content complexity and to reach an efficient division of for virtual slide microscopy images into tiles; providing both the conventional DICOM services and the image interchange using JPIP (JPEG2000 interactive protocol).

3. Automation in Pathology: Analysis of Scanning Solutions for Pathology Microscopic Slides

There are many recent solutions for whole slide scanning of histological sections and cytological slides [6]. We have reviewed different existing solutions and interviewed users of these systems with the aim of summarizing the possibilities of existing technology and the adequacy to user demands in education, research and clinical practice.

COST Action IC0604 WG4 has reviewed the twelve commercial scanning systems. Also, virtual slide viewers and upcoming related projects about managing large pathology images have been studied. After reviewing all existing solutions, we found the following actors to be important to be considered to integrate slide scanners in the daily workflow of pathology departments:

- a) Factors to be considered in the pre-scanning phase: compatible slide glass (size and thickness); slide handling or trays; number or slides and orientation: only horizontal trays are acceptable for frozen section slides; slide loading (speed and reliability); barcode reader (multiple barcode formats and multiple fields); focusing quickly and accurately on the specimen.
- b) Factors to be considered during scanning phase: color digital camera (sensor resolution and scanning method); automatic/manual scanning; Z-stack scanning; scanning time; anti-vibration performance; fluorescence scanning; objective lens, including focus accuracy with high powered lens and lens aberration.
- c) Post-Scanning factors: image processing algorithm, that makes a whole image with no dividing lines; image compression; slide format: JPEG, JP2, TIFF, BMP, or proprietary.
- d) Software included (Scanning Software to control the scanner, slide viewer, web viewer, slide database, workflow management)

Existing systems allow a high quality digitization of pathology microscopic images [7], although in some cases, obtained images still may contain out of focus areas, and the main complain of users is the delay in viewers to move between different fields and magnifications.

4. Application of Automated Quantitative Analysis in the Pathological Classification and Diagnosis of Inflammatory and Neoplastic Diseases

The relevance of density and/or distribution of various cells (e.g., neuroendocrine cells [NEc]) using immunohistochemistry markers need to be studied for a better understanding of some inflammatory and neoplastic diseases. Different image analysis methods that can be performed in static pictures and virtual slides need a consensus.

The automated image analysis was performed with the IAI software which was designed for recognition and counting the immunoreactive cells. (The team of researchers from the Warsaw University of Technology and the Military Institute of the Health Services). The software was used for evaluation the NEc density within the gastric glands of varies gastritis types, as well as for a study of the proliferation index (Ki-67) and tumoral cell density in some brain tumours (meningiomas and oligodendriogliomas).

Automated counting of cells density was performed on the digital images, at 400x, with the algorithm for the immunoreactive cells recognition which combines the

mathematical morphology operations and artificial neural network (SVM type). The software was prepared in Matlab language.

The automated image analysis results were compared with the manual reading results obtained by light microscopy semiquantitative measurement. Additionally for the Ki-67 Index study the comparative automatic quantitative analyses was done by the ImageJ algorithm with specific Ki-67 plug-in.

The comparative study on the quantitative automatic and semiquantitative light microscopy methods used for the immunoreactive cells recognition is the first step in the validation of the automatic quantification in immunohistochemistry of the digital pathology (virtual slide – based diagnostics).

5. Outline of the Workshop

The objectives of Coordinating research efforts on Digital Pathology workshop are discussing the work plan of COST Action IC0604 for telepathology in Europe and the health informatics standardization efforts in pathology performed by main standardization bodies. The program for the workshop is as follows:

- Thomas Schrader: Business processes in Pathology
- Christel Daniel: Informatics Standardization and IHE
- Vytenis Punys: Handling whole slide microscopy images in picture archiving and communication system
- Marcial Garcia Rojo: Virtual microscopy scanning technology
- Janina Slodkowska: Application of automated quantitative analysis in Pathology
- Final round table: Architecture of a European distributed health care environment for patient care and research in Anatomic Pathology Chair: Bernd Blobel

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