From virtual microscopy to systems pathology

A meeting report of the 1st European workshop on tissue imaging and analysis, Heidelberg, Germany, 13–14 February 2009

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Introduction

Virtual microscopy encompasses the high-resolution scanning of tissue slides and cell preparation and derived technologies including automatic digitalization and computational processing of whole microscopic slides, cytological preparations and tissue arrays, and web-based easy accessibility and analyses. For the first time, it enables high-throughput imaging and quantitative measurements of tissue structures. By integrating mass tissue data and derived analyses, virtual microscopy creates novel synergies between technological disciplines such as pathology/histology, bioinformatics, medical informatics, image analysis, as well as cell and molecular biology. These technical synergies may pave the way for new structures in research, clinical diagnostics, education, and training and fundamentally support newly arising disciplines like medical systems biology. The 1st European Workshop on Tissue Imaging and Analysis, held in Heidelberg on 13th and 14th February 2009 intended to provide a discussion forum for multiple disciplines related to virtual microscopy, like pathology, systems biology and pathology, computer-assisted high-throughput diagnostics, cell-based cancer diagnostics, bioinformatics and image processing, and the scientific exchange of key players in the field. Over 140 participants from 10 European countries as well as USA and Japan took part in the meeting.

Sessions

Research applications

Several speakers covered topics from tissue banking over the systematic evaluation of tissue morphology using image processing up to systems biological modeling of tissues. Niels Grabe (University Heidelberg, Germany) introduced virtual microscopy as a tool and its increasing role in Medical Systems Biology as it generates the necessary data of tissue morphology in which molecular computational models of diseases will be embedded. This has motivated the foundation of the first interdisciplinary institutions linking Pathology, Systems Biology, and Medical Informatics, such as the Tissue Imaging and Analyses Center at the University of Heidelberg [1]. Ulf-Dietrich Braumann (University Leipzig, Germany) presented how microscopy is presently undergoing a transformation due to the increasing availability of digital image acquisition devices. He demonstrated how growth of carcinoma of the cervix, prostate, and skin as well as regeneration processes and tissue formation, for example of nerves and joint cartilage, can be quantified using image data obtained by virtual microscopy [2]. Nobert Wey (University Zurich, Switzerland) showed what is needed to quantify Alzheimer plaque on virtual slides. His work provided an excellent example for the necessity of having an efficient work flow allowing
the automated analysis of high volume imaging data. 
Pascal Tomakidi (University Freiburg, Germany) provided
data on the use of virtual microscopy in epithelial tissue
cultures, especially how quantitative spatial profiles of
markers of epithelial homeostasis were generated. These
analyses may form the basis for prospective simulation
attempts of epithelia formation and regeneration [3].
Andreas Heffel (University Leipzig, Germany) reported
how automated image segmentation and classification
provide an indispensable requirement for a large-scale
analysis of in situ hybridization gene expression patterns
(GEP). He presented an automated process flow for
segmentation, classification, and clustering in large-scale
sets of Drosophila melanogaster GEP that is capable of
dealing with most of the technical problems implicated in
these images. Peter Schirmacher (University Heidelberg,
Germany) described tissue banks as essential platforms for
modern biomedical and translational research. Besides
tissue storage, distribution, project management, and
support in morphology-based techniques, tissue banks
offer an optimal platform for decentralized tissue-based
research projects, including centralized scanning of decen-
trally obtained stains, especially multi-tissue arrays, data
storage, and data analysis as well as decentralized access
to data, their analyses as well as reference slides. These
tools can be extended through further integration of additional
tissue technologies (e.g., fluorescence techniques) and
bioinformatics.

Industrial applications

Technical capabilities and the application potential of
currently available virtual microscopy technologies as a
key technology in industrial research were discussed by
several speakers. Maria Athelogou (Definiens, Germany)
described how “Intelligent Image Analysis” plays an
important role and moves into the heart of R&Ds and
Diagnostics. She stressed that accurate information from
image processing is critical for pathologists and oncologists
as it determines the predictive and prognostic outcome of
morphological studies. Niels Foged (Visiopharm, Denmark)
demonstrated that the quantitative analysis of the HER-2
immunostaining in breast cancer tissue sections represents
an important challenge for digital pathology. He introduced
a novel, highly discriminative algorithm for scoring HER-2
and thereby also presented the widely applicable principles
of image sampling, data management, and quantification in
whole slide images. Heinrich Bürgers (TissueGnostics,
Austria) sketched a novel approach to imaging, analysis,
diagnosis, and documentation of histological slides by the
use of FACS equivalents for cells in tissue slides and
smears. Catherine Conway and Lynn Dobson (Slidepath,
Ireland) showed quantitative data resulting from a study
using the application of image analysis as adjunct to
manual evaluation of HER-2 status. They described the
development of a HER-2 image analysis algorithm that
classified cases based on both the intensity and continuity
of membrane staining. The performance of the algorithm
was validated across a large cohort of clinical cases and
achieved a 91% concordance with manual review by a
pathologist. Agreement with gene amplification status as
the gold standard was also found to be higher for the
automated review, suggesting a potential of this technology
as a support to increase the diagnostic standardization of
HER-2 evaluation [4]. Lars Schmidt (Agfa, Germany)
described the technical requirements for the embedding of
virtual microscopy in a hospital setting as an example for
an administrative–medical workflow in the field of digital
pathology. Masafumi Oshiro (Hamamatsu Photonics,
Japan) elaborated on the basic concepts of virtual micros-
copy already introduced in 1997, since then becoming
rapidly an indispensable tool to support digital pathology
applications. Thereby, the technical implications of slide
scanning determine the potential of virtual microscopy.
Furthermore, new features, such as virtual fluorescence
slides and Z-stack for focusing, were presented, which may
enable the introduction of novel clinical applications.

Education and training

Research and training represent the areas where virtual
microscopy has first entered practical application, and in
this field, the most advanced experiences exist. Jim
Diamond and Peter Hamilton (Queens University Belfast,
Ireland) noted that we currently experience a tipping point
in tissue-based research and education [5]. The importance
of pathology diagnostics as a central discipline for
translational research and biomarker discovery was
stressed, and the technical challenges including storage,
remote slide viewing, and high-performance image pro-
cessing were sketched. From this, novel opportunities for
application in education, quality management, tissue ar-
chiving, and research were elaborated. Peter Riegman
(Erasmus Medical Center, Rotterdam, The Netherlands)
showed how virtual microscopy is increasingly replacing
conventional microscopy in students training at Rotterdam
Medical School. He reported VM to enable teachers to
spend more time on teaching and collaboratively discussing
histology and pathology topics. He also showed that
students appreciated virtual microscopy far more than
conventional microscopy, Alberto Pérez-Bouza (RWTH
Aachen, Germany) demonstrated his innovative approaches
and experiences when implementing virtual microscopy in
histology courses since June 2006. He analyzed the
acceptance of the web-based digital microscopy by ques-
tionnaires filled out by students and also by an analysis of
the number of visits on the web server. He found that students not only appreciated the possibility of learning microscopy through the Web but also used the system intensively for training purposes and self-assessment prior to examinations. Moreover, the integration of the virtual histology into a video podcast containing macroscopic images, drawings, etc. has improved the acceptance of clinical pathology as an attractive and modern subject. Katharina Glatz (University of Basel, Switzerland) presented Pathorama as a publicly accessible modular e-learning platform used at all levels of pathology education, including a searchable atlas containing more than 600 virtual slides. Various contributors have fed categorized metadata including the slide URL into the central slide database while the slides are stored on servers at the contributing institutes [6]. Marco Novelli (University College London, Great Britain) reported positive experiences of applying the virtual microscopy technology, including fast remote virtual slide access; reported improvements were benefits in the quantitative measurements of virtual slides (Breslow’s thickness measurement, proliferation index), remote reporting, and greatly improved e-learning. He also elaborated on difficulties like hospital firewalls, the need of technical education, as well as relatively high costs for image processing, storage, and scanning.

Clinical applications

Peter Hufnagl, Karsten Schlüns, and Norman Zerbe (University Berlin-Charité) discussed the basic requirements for the use of virtual microscopy in routine pathology. Despite being widely accepted in Pathology for educational purposes and teleconsultation, they stated that the broad routine use of VM in surgical pathology is currently not in sight due to the technical requirements and some further limitations. Instead, they identified application potential in the fields of education, second opinion, and interdisciplinary tumor centers, routine marker quantification for small departments as well as large university institutes [7]. Furthermore, the rise of tumor centers is expected to promote the routine use of VM. In conclusion, similarities to digital radiology were identified although the introduction was estimated to take some years. Peter Sinn (University Heidelberg, Germany) reported recent experiences in the application of virtual microscopy in reference pathology and external clinical services. Telepathology and teleconsultation were presented as important application fields. He showed results from a diagnostic trial in cryosection evaluation. He concluded that telepathology is almost equivalent to conventional microscopy in the evaluation of frozen sections if no evaluation of the macroscopic aspects of the specimen is required, e.g., in the frozen section diagnoses of sentinel lymph node biopsies [8]. Thomas Fuchs (ETH-Zürich, Switzerland) presented a framework for biomarker quantification using tissue microarrays based on experiences with clear cell renal cancer by computational pathology including correlation with survival analysis [9]. Quantified histological assessment of human tissues was identified as the key point for the automation and objective assessment in predictive pathology. Manfred Schmitt and Lena Seiz (Technical University München, Germany) reported on the assessment of Urokinase plasminogen activator (uPA) and its inhibitor (PAI-1) which are accepted predictive markers in breast cancer by virtual microscopy. Automated scanning, followed by computer-assisted quantitative scoring of uPA and PAI-1 immunohistochemistry, may represent a potential alternative to the established ELISA measurements, recently recommended for clinical application in the ASCO guidelines 2007. Niels Halama (National Center for Tumor Diseases, University Heidelberg, Germany) presented a quantitative analysis of immune infiltrates in primary colorectal cancers and their liver metastases. Quantitative cell counts based on immune cell surface molecules (CD3, CD8, Granzyme B, and CD45RO) were independent predictors of patient outcome. Using virtual microscopy, the intratumoral heterogeneity of the investigated immune cells was assessed. Computational simulation of tissue microarrays from the virtual slides showed that intratumoral heterogeneity of all measured surface molecules was so high that a reliable measurement of the surface molecules for an individual patient was only achieved by analysis of full-size tissue sections. He suggested studies for the definition of potential biomarker cutoffs. Potential diagnostic tests should include quantitative assessments of intratumoral heterogeneity. This could be reliably achieved by measurements in full-size tissue slides using virtual microscopy [10]. Thomas Schrader (University of Applied Sciences, Brandenburg, Germany) elaborated on the need for standardization when embedding virtual microscopy in the Integrated Healthcare Enterprise [11]. A communication concept was presented connecting virtual slide scanners and pathology laboratory information systems. Nicolas Wentzensen (National Cancer Institute, Bethesda, MD, USA) presented the innovative application scenario of virtual microscopy in cervical cancer screening cytology. Virtual microscopy has the potential to improve this process at several levels. Novel biomarkers allow the automated detection of abnormal cells with increasing sensitivity and a reduced evaluation time. Web-based evaluation allows cytopathologists to analyze specimens without the need for circulating glass slides. Archiving of digital microscopy images preserves slides under optimal conditions and saves storage space.
Conclusions

The workshop provided a comprehensive overview over novel technologies and applications of virtual microscopy and a forum for stimulating interdisciplinary discussions, representing diverse fields such as pathology, computer sciences, systems biology, biomedical informatics, biotechnology, epidemiology as well as basic biomedical research. It is intended to be pursued in a regular, most likely annual format.

References


The given references do not reflect the contents of the individual talks but provide further information concerning that matter.