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Quantitative Bioimaging: Signal Processing in Light Microscopy

Microscopy has historically been an observational technique. In recent years, however, the development of automated microscopes, digital sensing technologies, and novel labeling probes have turned microscopy into a predominantly quantitative technique. In this context, the management and analysis of automatically extracted information calls for the involvement of signal and image processing experts to provide technically sound, quantitative answers to biological questions. This is especially relevant today, due to the widespread use of time-lapse video microscopy, high-throughput imaging, and the development of novel superresolution microscopy techniques. The complexity and size of the multidimensional and often multimodal data produced by those microscopy techniques requires the use of robust computational methods encapsulated in advanced bioimage informatics tools.

Our motivation for publishing this special issue of *IEEE Signal Processing Magazine* is to stimulate the interaction among researchers from the biological, optical, computer science, and signal processing communities by 1) presenting cutting-edge signal processing research in quantitative bioimaging and 2) bringing the vast scope of ongoing open problems and novel applications to the attention of the signal processing community. As we hope to show in this issue, there are many high-impact signal processing challenges at the intersection of quantitative bioimaging and integrative biology where signal processing experts can make a mark. These challenges are described in the context of the imaging modality used, the probes and sensors employed for image acquisition, and the final targeted applications (i.e., development studies, disease diagnosis and prognosis, drug discovery). When possible, works following the reproducible research (http://reproducibleresearch.net) philosophy are highlighted.

The interest that the signal processing community has in quantitative bioimaging is evident from the increasing number of papers submitted on this topic to signal processing-oriented publications, workshops, and conferences. Dedicated issues on molecular and cellular bioimaging were previously published in *IEEE Transactions on Image Processing* [1] and *IEEE Signal Processing Magazine* [2]. The rapid evolution of the field justified the interest of devoting a new special issue to examine all these developments from a signal processing perspective. Furthermore, in the last few years, a number of related "scientific challenges" have been held either as stand-alone or as part of image processing conferences. These activities are very relevant for the community since they facilitate the comparison of various algorithms for a given generic task (e.g., deconvolution, single particle localization, particle tracking, cell tracking) using a normalized framework consisting of annotated data and common evaluation metrics. In terms of funding programs, the importance of quantitative bioimaging research is also apparent. In this respect, the European Strategy Forum on Research Infrastructures roadmap contains a pertinent project, "Euro-Bioimaging," with a dedicated work package on data storage and analysis. The U.S. counterparts of the European initiative are the "Continued Development and Maintenance of Software" program run by the U.S. National Institutes of Health (NIH), since 2002, and the recently announced "Software Infrastructure for Sustained Innovation" program that will be run by the U.S. National Science Foundation (NSF). Apart from those, a number of consortia addressing extraordinarily relevant problems are being or will be funded by the European Union (under the Seventh Framework and the recently opened Horizon 2020 Programmes) and the NIH and NSF. All of these provide ample proof that this issue's theme is timely, and we hope that it offers barrier-breaking material from which the readership will benefit.

From a systems biology perspective, the cell is the principal element of information integration. Profiling cellular responses and clonal organization in its spatiotemporal context are important endpoints for unraveling molecular mechanisms of diseased tissue (e.g., bacterial invasion, cancer). The first article, "Toward a Morphodynamic Model of the Cell," by Ortiz-de-Solórzano et al., is a review of relevant signal processing aspects from the detection of cellular components to the description of the morphodynamics of the entire cell in relation to its extracellular environment. A survey of ongoing efforts to create a credible model of cell behavior is also an integral part of the manuscript. Significantly related, Dufour et al. in "Signal Processing Challenges in Quantitative 3-D Cell Morphology" give an overview of the problems, solutions, and remaining challenges in deciphering the morphology of living cells via computerized approaches, with a particular focus on shape description frameworks and their exploitation, using machine-learning techniques. In their technical article, "Snakes on a Plane," Delgado-Gonzalo et al. present an extended and inclusive taxonomy of different variants of two-dimensional active contours (also known as *snakes*) for the

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segmentation of cells and other biological entities. The authors also lay out general design principles that can help to create new parametric snakes adjusted to different imaging modalities.

Newly developed superresolution microscopy techniques break Abbe's diffraction limit, providing lateral resolution values as high as 10 nm, far below the 250 nm of conventional microscopy. Those techniques, through the visualization of molecular machinery, are helping to answer biological questions about the mechanisms of cellular behavior regulation. Localization microscopy is one of these superresolution techniques. In localization microscopy, the fluorescent labels are photochemically manipulated to switch "on" and "off" stochastically, such that at each instant in time only a sparse subset of all molecules is in the "on" state in which they fluoresce. Assembling the localization data obtained from all frames into the final superresolution image reveals previously hidden details. In "Image Processing and Analysis for Single-Molecule Localization Microscopy," Rieger et al. describe the image processing and workflow involved, from raw camera frames to the visualization and quantitative analysis of the reconstructed superresolution image. Single-molecule approaches place stringent demands on experimental and algorithmic tools due to the low signal levels and the presence of significant extraneous noise sources. This necessitates the use of advanced statistical signal and image processing techniques for the design and analysis of single-molecule experiments. In their article, "Quantitative Aspects of Single-Molecule Microscopy," Ober et al. address this issue and discuss the resolvability of single-molecule localization from an information-theoretic perspective.

The use of time-lapse video microscopy to capture the spatiotemporal dynamics of many biological experiments has significantly increased. The complexity of those experiments is driving continued advances in the incipient field of bioimage informatics [3]. Registration, segmentation, and annotation of microscopy images and respective biological objects (e.g., cells) are distinct challenges often encountered in this field. In "3-D Registration of Biological Images and Models," Qu et al. discuss several studies in widely used model systems such as fruit fly, zebrafish, or *C. elegans* to show how registration methods help solve challenging segmentation and annotation problems for three-dimensional cellular images.

A classical light microscopy application in clinical practice is histopathology. Clinicians evaluate histological preparations for the patient's diagnosis, estimation of prognosis, personalized therapy planning and, in a research context, biomarkers discovery. Tissue processing for histology is increasingly automated, and digitalization using modern computer-driven microscopes or slide scanners is extremely time effective and generates an extensive volume of data. Therefore, as described by McCann et al. in "Automated Histology Analysis," there is a niche for image analysis methods that can automate prohibitively time-consuming tasks for human evaluation. Moreover, as concluded by the authors, a close collaboration and extensive work with pathologists is required for the developed applications to reach an important impact in clinical practice.

The final article, "Optical and Optoacoustic Model-Based Tomography," by Mohajerani et al., describes optical imaging techniques that reach beyond microscopy depths, bringing unique visualization of intact small animals or human tissues in vivo. Light propagation in tissue defines complex nonlinear inversion problems in both optical and optoacoustic model-based tomography. Therefore, the robust localization and quantification of the optical probes is a nontrivial problem opening up a clear opportunity for the signal processing community.

We would like to express our appreciation to the editorial board and staff of *IEEE Signal Processing Magazine* (particularly Special Issue Area Editor Fulvio Gini) for encouraging, reviewing, and facilitating the process of editing this issue. It would not have been possible without the high-quality feedback received from the conscientious reviewers whom we wish to thank for their volunteer efforts and timely responses. We sincerely hope you enjoy reading this issue as much as we enjoyed putting it together.

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